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SOME CONSIDERATIONS ON HEAD INJURIES.[1]

BY DONALD ARMOUR, C.M.G., F.R.C.S.

THE practical interest and importance of the subject of head injuries, concerning as it does in its varied aspects almost every branch of our profession, cannot be denied. Among both surgical and neurological problems there is none which presents greater difficulties of decision than the treatment of head injuries. The great variety in the types of injury and of the disturbances of function which may occur, and the relatively greater or lesser importance of such injury according to its degree or localization, all combine to make impossible the laying down of any rule in the treatment of such cases. The treatment concerns not only the immediate recovery of these cases, but also the future condition of the patient. It should not be limited, therefore, merely to the saving of the patient's life, but it should aim at obtaining as normal an individual as before the receipt of the injury.

John Bell, writing a century and a quarter ago, thus expressed what will be my main thesis of this evening:—

"And we have this encouragement to consider the pathology in place of the anatomy of the skull, as the rule of our prognostics, that while anatomy and the enumeration and classification of fractures has led to an undue propensity to operation, the study of the living powers, and the mutual dependence of these parts, leads to a reserved, modest and rational practice—to a just confidence in the powers of Nature—to a careful and solicitous attention to all the insidious symptoms of an injured brain."

And in our own time the same plea has been made by Wilfred Trotter, who says:—

[1] Presidential Address delivered to the Neurological Section of the Royal Society of Medicine, on October 11, 1928.

"In the case of head injuries it is of cardinal importance that diagnosis and treatment should be kept in a close and living association with pathology. In every case it is essential that the surgeon, before attempting to begin the treatment, should make a determined effort to call up the clearest possible picture of the actual conditions within the skull of the patient he has to deal with."

This injunction should be in the mind of every surgeon who may be called upon to deal with head injuries.

Unfortunately, in the past and even up to the present, the subject of head injuries in our textbooks on surgery appears in the section on "Fractures," and thus early the mind of the medical man is imbued with an exaggerated importance of the "enumeration and classification" of fractures of the skull to the detriment of a proper appreciation of the much more important part of the subject, viz., the damage, functional or organic, that the contents of the skull may have suffered. This is constantly revealed by the early insistence upon an X-ray of the skull being taken after a head injury, as if the presence or not of a fracture of the skull were the important factor in the case, and as if the result of the radiograph would be sufficient to determine by what means and methods the associated cerebral injury should be treated. Moreover, its very use constitutes at times a pitfall in the prognosis of a head injury because of the false importance attaching to the presence or absence of fracture of the skull, its absence always presuming a better prognosis than its presence. For the same reason there is a widespread lack of appreciation of the importance of so-called minor head injuries. "Minor" perhaps in the estimation of the patient and of his doctor, but so often "major" in its later manifestations and sequelæ. It is to this aspect of the subject, viz., head injury without fracture, that I wish to deal.

A general increase in intracranial pressure is the commonest result of a severe head injury. This is brought about in the first instance by reactionary œdema or hæmorrhage, or both. Later, this increased pressure may be aggravated or maintained by interference with the paths of absorption of the cerebro-spinal fluid by the swelling or displacement of the brain itself. This swelling or displacement acts first by blocking the cerebral subarachnoid spaces, and as a result the cerebro-spinal fluid collects in the basal cisterns and in the ventricles.

The enlargement of the basal cisterns forces the midbrain up, occluding the narrow space of the incisura tentorii. The swollen brain with its distended ventricles pushed up against the resistant dura inter-

feres still more with absorption, and so a vicious circle is established. Added to this, we have the direct pressure on the medulla of the fluid in the basal cisterns. The sum of all this mechanical pressure is exerted upon the blood-vessels of the brain, either locally or generally, giving rise to focal or widespread symptoms.

Such is the result at any rate of a severe injury. Can the same factors, in a lesser degree, explain the symptoms associated with or following upon a so-called minor injury?

The term "concussion," according to Trotter, should be used "to indicate an essentially transient state due to head injury which is of instantaneous onset, manifests widespread symptoms of a purely paralytic kind, does not as such comprise any evidence of structural cerebral injury, and is always followed by amnesia for the actual moment of the accident."

Two exceptions may be taken to this classical definition of concussion. Is it possible to affirm that the state is essentially transient, unless we limit the expression strictly to the unconsciousness and the immediate paralytic phenomena associated with it? Is it correct to affirm that concussion of the brain "does not as such comprise evidence of structural cerebral injury?"

How are we to explain the onset and persistence of those post-traumatic symptoms which are so often included under the misnomer "post-concussion neurosis"? Undoubtedly, they are largely the direct expression of disturbances of intracranial pressure; this disturbance being commonly in the direction of hypertension, though in some few cases hypotension has been found.

Cassasa explains the mechanism of concussion as depending upon the existence of "a network of fine fibrils connecting the external wall of the blood-vessels with the surrounding brain tissue across the perivascular lymph spaces." It is conceivable that any sudden overfilling of the perivascular lymph spaces with cerebro-spinal fluid could produce laceration of a vessel by the tearing of its wall in the neighbourhood of such a fibrillar attachment

On the other hand, without such an attachment the laceration of a vessel surrounded by fluid could not be produced by any pressure exerted through that fluid, which would tend to compress the vessel but not to lacerate it. Such an increase of cerebro-spinal fluid in the perivascular lymph spaces could be caused by the cerebro-spinal fluid from the surface of the brain being driven into it by the pressure exerted by the change of shape of the skull as the result of a blow or a fall.

This change of shape under an area of violence is in the direction of flattening and diminution of space for the cerebro-spinal fluid in that area. This fluid must find its way out of that area through the various sulci of the brain, and such fluid as cannot find its way through these channels must find a way into the perivascular lymph spaces in the reverse direction of the normal flow of the fluid in these channels. Now Weed's experiments have demonstrated that the perivascular lymph sheath—the Virchow-Robin space—is directly connected with the finer spaces about the central ganglion cells.

Cassasa suggests that sudden physical distension of these peri-ganglionic spaces by cerebro-spinal fluid in cases of concussion causes a direct physical change in the ganglion cell, which may explain all the phenomena of concussion of the brain. He thinks these simple changes may occur without minute hæmorrhages, and explains the completely negative findings at post-mortem examination in many cases of concussion.

Osuati and Giliberti go further in emphasizing the structural factors in concussion of the brain. Basing their opinion upon the study of 100 cases of concussion, they conclude that not only is there actual cerebral injury in concussion, but in a few instances complete resolution does not occur, and that there is a strong likelihood that secondary degenerative changes develop. They suggest the term "traumatic encephalitis" in place of "post-concussion neurosis."

Whether these engaging theories are capable of proof or not, there can be no doubt that the symptoms usually following concussion—the commonest of which is headache of varying quality—are the expression of an altered pressure of the cerebro-spinal fluid. Not only a stable alteration in pressure in one or other direction, but an instability of pressure such as has been described in epilepsy, would seem to be the cause in a certain number of cases.

Mestrezat, Bouttier and Logre found in 80 per cent. of a large number of cases of concussion without head wounds definite changes in the cerebro-spinal fluid. The essential features were an increase in tension and an excess of albumin, while the chlorides were normal, the sugar rather increased, fibrin absent and the permeability normal. The interpretation placed by them upon such a fluid was that it was due to an aseptic disintegration of nerve tissue without meningeal involvement, combined with a marked tendency to hypersecretion.

This "formula of concussion" is also characterized by its evolution, the excess of albumin usually appearing at the end of two to three days,

and disappearing as a rule at the end of some weeks or months with return to normal. Sometimes there was an indefinite persistence, or a slow regression of the syndrome during a number of months.

They would use this "formula" for the diagnosing of an "associated concussion" in cases when no evidence of a head injury was adduced, but at the same time they would not exclude concussion owing to the absence of an anomalous cerebro-spinal fluid. A caution, however, is necessary in cases of associated nerve contusion giving the additional signs, more or less marked, of a meningeal hæmorrhage. From a medico-legal point of view, the possible imitation of their formula in syphilis of the nervous system is of the greatest importance, calling for a Wassermann test in cases showing a lymphocytosis, however slight.

In confirmation of these findings, Claude, Lamache and Dubar have lately carried out similar investigations on the cerebro-spinal fluid of patients who had suffered from head injuries without fracture of the skull. Very few of them had total loss of consciousness. The time intervening between the receipt of the injury and the examination of the fluid varied from two or three weeks to several months. These patients sought relief on account of such subjective symptoms as headache, dizziness, weakness, insomnia, tinnitus aurium and visual fatigue. Increase in albumin was found in nine out of the twenty-two cases examined, the excess tending to disappear gradually as the symptoms subsided after repeated lumbar puncture. Otherwise the fluid showed no chemical nor cytological abnormality. But the tension of the cerebro-spinal fluid was found altered in all the cases except five. The alteration took the form of hypertension, hypotension or instability of tension, the first being most frequently found.

What explanation can be offered for such alterations in the tension of the cerebro-spinal fluid following head injury? Obviously the increase following immediately upon a severe injury, with associated œdema or hæmorrhage, or both, is due, very largely at any rate, to mechanical causes. These have been described already.

The increase in tension following upon slight injuries and maintained over a considerable period may be due to such factors, acting alone or in combination, as:—

(1) Increase in the amount of cerebro-spinal fluid secreted.

(2) Interference with its circulation and absorption.

(3) Variations in volume of the cranial contents, nervous, ventricular and vascular.

Granting that the choroid plexuses are the chief source of the cerebro-spinal fluid, whether the process be a secretion or a transudation, or, according to Mestrezat, a mere dialysation from the blood, can we find any conditions associated with or following upon cerebral trauma which will activate or inhibit this process?

The Effect of Trauma upon the Choroid Plexuses.

The system of the ventricular cavities and their contained cerebro-spinal fluid has been said to be of importance in determining the distribution of force within the skull. The position of the choroid plexuses would thus render them particularly vulnerable, and expose them to the direct action of the wave of repercussion at the time of the accident. Can such trauma, if it occurs, affect their secretory activity?

Some writers would invoke an altered fluid, following upon microscopic vascular and nervous lesions and meningeal irritation, as being the cause of a secondary or reactionary hypersecretion.

Duret thinks that trauma causes a cerebro-spinal shock, giving rise to disturbances of the cerebro-meningeal circulation, tending to a congestion of the brain mass and producing intracranial hypertension by lessening the cranial space, by venous stasis and by augmentation of the circulation with increased flow of blood to the secretory organs, i.e., the choroid plexuses. In addition, he postulates an irritation of the meninges, ependyma and plexuses by the waste products of disintegration in cases of minute pial hæmorrhages and of post-congestion extravasations, a selective poisoning as regards function by the products of breaking-down nerve tissue as a result of microscopic tears and contusions. In short, he would attribute hypertension to hypersecretion of cerebro-spinal fluid.

The causes of hypotension are equally hypothetical. Apart from that due to the loss of cerebro-spinal fluid from trauma, following lumbar puncture and at operations, all of which give rise to a sudden hypotension, there remain the occasional cases following head injury, in which the hypotension manifests itself, usually at a later date, by definite clinical symptoms. These may be, according to Leriche, intense frontal headache, dizziness, nausea, sometimes convulsive phenomena, stupor and even coma.

In head injuries, Leriche would explain the hypotension as due to the formation of a porencephalic cyst on the surface of the brain, a

sort of supplementary sub-arachnoid cistern, resulting in a relative insufficiency of cerebro-spinal fluid and a consecutive hypotension. Most probably several factors may be responsible, such as a functional disturbance of the regulating centre of fluid tension, inhibition of the cells of the choroid plexuses, or local modifications of the cerebral circulation.

Förster and Wartenberg have called attention to certain changes in the shape and position of the ventricles following upon head injuries. These changes were chiefly in the nature of a distension or dilatation of one or both lateral ventricles, with a stretching of their summits in an upward and outward direction. The dilatation was usually greater on, or confined to, the side of the lesion—hydrocephalus internus lateralis—and the ventricle was drawn up towards the site of the lesion—"Ventrikelwanderung." This unilateral appearance may be met with in the absence of unilateral clinical findings. According to Förster, this wandering of the ventricle takes place slowly and gradually. The final result is a thin membrane comprised of arachnoid, pia and the remains of the cortex covering a dilated ventricle, which he calls a traumatic porencephaly.

Wartenberg describes as an end-result of commotio cerebri a condition characterized by numerous areas of hæmorrhages or softening, a persistent and progressive cicatricial shrinkage of the whole brain and an alteration in the shape of the ventricle, the latter dilating at the expense of the brain substance (passive hydrocephalus). He describes the whole brain as being drawn from its central position towards the side of the lesion—"Gehirnwanderung."

This passive hydrocephalus may be converted into an active one by a traumatic meningitis serosa ventriculi, causing an irritation of the choroid plexus with an increased secretion of cerebro-spinal fluid.

Both these authors make a plea for the routine use of ventriculography (encephalography) in late cases of head injuries, particularly if operation is contemplated. Several of their cases are reported as being very greatly improved as a result of the ventriculography alone.

Block and Oppenheimer have made a comparative study of the intraspinal pressure, blood pressure and intra-ocular pressure in head injury. In eleven cases of fracture of the skull, although the blood-pressure was below the average, the spinal pressure was above normal and the ocular pressure was above the average. They conclude that "no individual parallelism exists between intraspinal pressure, arterial pressure and ocular tension," but on an average a high pressure of one

type is associated with a high pressure of the other types; the same is true of low pressure.

Any attempt to estimate clinically intracranial pressure in the light of general blood-pressure findings is not of practical value. The presence of initial shock following a severe head injury and lasting for some hours, associated as it is with a fall in the general blood-pressure, will mask the true intracranial condition. Again, the intracranial pressure must reach a very dangerous stage of compression before it can affect the general blood-pressure in the direction of any marked increase.

Both in the acute and chronic stages of a head injury the value of the determination of the pressure of the cerebro-spinal fluid is beyond question. The estimation of this pressure to be of any accurate value must be made with a manometer. Attempts to estimate the pressure by counting drops per unit of time, or by the force with which, or the distance to which, the fluid spurts, are equally fallacious. Too many extraneous factors may be the cause of invalidating such conclusions.

It has been said that "normal pressure may be almost anything," and it must be admitted that normal pressure has certainly a wide range. Ayer places a normal pressure between 100 and 200 mm. of water, regards as "suspiciously high" pressures between 200 and 250 mm., and as "definitely abnormal" those between 250 and 300 mm. Pressures over 300 mm. are always to be explained on the basis of intracranial pathology.

The presence or absence of blood in the cerebro-spinal fluid following head injuries is often stressed beyond its true clinical significance. Its presence is only of importance as a corroborative sign of intracranial injury associated with bleeding from an intradural vessel. Its absence, however, does not exclude intracranial hæmorrhage, even be it subdural or subarachnoidal. From the point of view of treatment, neither the presence nor absence of blood in the cerebrospinal fluid has any importance whatever. The *pressure* of the fluid as an indication of the degree of intracranial tension is the all-important matter.

The eyes in head injury.—Immediately following upon the receipt of injury, the pupils are more or less dilated, depending upon the degree of the initial shock, and their reaction to light is correspondingly sluggish. During unconsciousness both these conditions are increased. As the stage of shock passes off the pupils usually return to their normal size and react to light, unless there be a definite increase in intracranial pressure, when the dilatation and sluggishness may remain. The pin-

point pupil in the early stage of a supracortical hæmorrhage or œdema passes into dilatation as the stage of irritation passes into the paralytic stage.

Injury to cranial nerves occurs in about 12 per cent. of head injuries, usually in basal fractures. The order of frequency would appear to be the seventh, sixth, eighth, third and second, the remaining ones being rarely involved. The frequency of combined involvement is not very great; the nerves lying close together are usually involved (seventh and eighth; second, third, fourth and sixth) by single fissure fractures; while in multiple fissures the groups, both as to the nerve involved and the side affected, are very irregular.

Varying conditions are concerned in the production of these paralyses of the cranial nerves. Probably the most frequent cause is injury of the nerve by bony compression, more rarely by laceration from displacement of the walls of the foramen. Where there has been no bony displacement, injury by bruising or laceration of the nerve sheath, with more or less severe reaction, may have occurred. Certain cases are possibly due to compression from a meningeal hæmorrhage.

But I wish to refer more particularly to the effect of increased intracranial pressure in the production of cranial nerve symptoms, more especially papillœdema, or perhaps more correctly "papillary stasis," as French neurologists call it. Cushing and Bordley some years ago showed by experiment how rapidly a retinal œdema may be made to appear in association with certain forms of increased intracranial tension, particularly when the compression is brought about by the introduction into the cranial cavity of fluid under tension; and how rapidly also the œdema may disappear when relief from tension has been afforded.

In practice it should be remembered that great assistance in estimating the grade of intracranial tension may be obtained by an examination of the fundi, for in head injuries with increased tension there may be a degree of papillœdema proportionate to the severity and duration of the intracranial symptoms.

Early signs are dilatation of the retinal veins with venous stasis, and œdema not sufficient to be described in terms of diopters. But with increasing tension there occurs an œdematous blurring of first the nasal margin and then the temporal margin of the disc, followed even by obscuration of the whole disc. As would be expected, fractures beneath the tentorium cause these changes more rapidly than those elsewhere. It is unusual, however, for these changes to appear within the first six hours.

In cases of local compression, but not when the tension is equally raised in all parts of the cranial cavity, the examination of the discs may be of great aid in determining the side on which the primary focal compression is being exercised. This unilateral intracranial stasis may have confirmatory evidence in the condition of those extracranial vessels which empty into the cranial sinuses, as shown by a dilatation of the vessels of the scalp, forehead and eyelids, and even a slight degree of exophthalmos.

Pidoux, in his study of increased intracranial tension present some time after the receipt of the injury, calls attention to the frequent occurrence of a bilateral papillary stasis, which is independent of any basal fracture or compression by effusion. With the relief of the tension the discs return to normal.

Turning to the more practical side of my subject, I would make a plea for the more frequent use of lumbar puncture as a therapeutic measure in both acute and chronic head injuries. I do not think its value is very generally appreciated. While in no way a substitute for a decompressive operation in cases of high intracranial tension, and even dangerous in some cases owing to the risk of medullary compression at the foramen magnum, in milder cases of increased tension the slow withdrawal of fluid, repeated if necessary, is of very great value. It very often allows the postponing of an operation until all the conditions are suitable, or even dispensing with it altogether. But the pressure of the fluid, not the quantity withdrawn, is the determining factor as to the further conduct of the case.

Again, in cases obviously not requiring the major operation of decompression, but suffering from severe headache, extreme restlessness, irritability, vertigo, etc., repeated lumbar puncture is of the greatest value in mitigating or curing these distressing symptoms. Therein lies the value of the so-called "spontaneous decompression" in fractures of the skull, with leakage of cerebro-spinal fluid. A value, unfortunately, too often offset by the ever-present danger of infection.

We owe to Weed and McKibben the knowledge that it is possible to lower the cerebro-spinal fluid pressure by the intravenous injection of hypertonic solutions, and conversely to increase the brain mass as well as the intracranial pressure by using hypotonic solutions. Haden, using a concentrated glucose solution, was the first to apply this knowledge clinically, while Cushing and Foley showed that the same results, though less pronounced, could be obtained by oral or rectal administration, which caused less disturbance of respiration and circulation.

Foley and Putnam believe that the decrease in intracranial tension is not due solely to decrease in brain volume, but primarily represents "new ratios between secretion and absorption of cerebro-spinal fluid."

Weed and Hughson, as a result of more extended experiments, conclude that, while the normal cerebro-spinal fluid pressure is partially dependent upon cerebral venous pressure and to a lesser extent upon cerebral arterial pressure, it is for the most part independent of either. And further, that the alterations in cerebro-spinal fluid following intravenous injection of hypertonic solutions, while partially parallel to the variations in cerebral arterial and venous pressures, are mainly independent of them and show much more marked depressions.

Fay found that the intestinal instillation of magnesium sulphate was almost twice as efficient as sodium chloride for the reduction of intracranial pressure. He attributes this to the fact that magnesium sulphate is non-dialysable, while sodium chloride is readily dialysed. He also points out that the administration of sodium chloride may produce a secondary wave of œdema and increased intracranial pressure, due to its absorption and immobilization in the tissues, with a subsequent attraction of fluid from the blood-stream. Fay calls attention to the fact that over-dehydration is possible and may be serious, if not fatal.

Howe has undertaken a series of experiments with the object of determining what solutions were least toxic and most efficient in lowering intracranial pressure when given intravenously. He tested a dozen hypertonic solutions; some were found too toxic and others relatively ineffectual. He found that sodium chloride produced the most pronounced decrease in intracranial pressure of any substance used, but is toxic unless administered very slowly. He, however, regards it as unfit for general clinical administration, on account of its immobilization in the tissues producing a secondary wave of œdema.

He found that dextrose is absolutely non-toxic and never resulted in the slightest disturbance of respiratory or cardiac action, no matter how much or how quickly it was given. 50 c.c. of a 100 per cent. solution given in less than a minute had no untoward action. He concludes that "dextrose is the only substance of this group which is non-toxic and produces a satisfactory fall in intracranial pressure."

The practical application of these measures for the relief of increased intracranial tension, whether in acute or chronic head injuries, is too obvious and too well known to require further comment.

Turning to the subject of surgical intervention in acute injuries we

are met with the problem of deciding, first whether an operation is advisable, and secondly, if so, when it should be performed. In about two-thirds of the cases of head injury there is little or no increase of intracranial tension and consequently no operation is indicated. In a certain number of others the injury has been so severe that the initial shock is combined with a rapidly appearing medullary œdema and collapse, making surgical intervention not only useless but reprehensible. We are left, however, with a remaining group in which only careful and repeated observations can determine what course we should pursue.

It may be said at once, and I desire to lay great stress upon this point, that no operation of any kind should be performed whilst the patient is in the condition of severe initial shock. It increases that shock and takes away whatever chance the patient may have had of recovery. All efforts should be directed at first to the treatment of the shock along the well-recognized lines. Again, should the patient have been allowed to pass into the terminal stage of medullary œdema and collapse, shown clinically by respiratory paralysis, with rapid and irregular cardiac action, widely dilated pupils, profound coma, complete muscular relaxation and a permanent fall in blood-pressure, no operation should be performed. These patients die, operation or no operation, and intervention only brings surgery into disrepute.

On the other hand, merely because of the absence of the usual and classical signs of fracture of the skull (bleeding and leakage of cerebro-spinal fluid from the ears or nose, subconjunctival hæmorrhages, &c.), and a negative radiograph in the presence of a greatly increased intracranial pressure, not to advise an operation is equally to be condemned. However, in the absence of such an increase of intracranial pressure, the presence of cranial nerve paralyses, of acute paralytic conditions and of convulsions, unless of a severe and persistent character, is not an indication for operation.

The ideal period for surgical intervention in acute head injuries is the "stage of capillary anæmia," when the increasing cerebro-spinal fluid pressure approximates to the capillary pressure. This stage is shown clinically by a slow pulse and a slight rise in the general arterial blood-pressure due to stimulation of the vasomotor centre. The increasing venous stasis is shown by severe headache, restlessness and even delirium, and a definite cyanosis appears. On ophthalmoscopic examination the retinal veins are seen to be large and dilated, with or without œdema of the discs. The pressure of the cerebro-spinal fluid as measured by the manometer will be 300 mm. or higher. It may be

added here that it is of the greatest importance to observe whether the degree of coma varies with the variations of the cerebro-spinal fluid pressure. Operation in the stage of capillary anæmia should be undertaken with a view to forestalling the onset of the major symptoms of medullary compression.

This operative procedure takes the form of a right subtemporal decompression. It has several advantages due to its anatomical relations. The squamous portion of the temporal bone is the thinnest part of the vault of the skull, and as such the easiest of removal. Its removal exposes the middle meningeal artery. The most important advantage, however, is the fact that the part of the brain lying beneath the decompression opening is the temporo-sphenoidal lobe, a "silent" area. In addition, it allows of the drainage of the middle fossa of the skull at its lowest point.

The simplest operation is performed by means of a horseshoe-shaped flap, which is turned down by an incision which commences above and behind the external angular process of the frontal bone, is carried along just below the line of the temporal crest, and curving downwards ends just behind the top of the ear. This flap should include everything down to the bone. The skull is trephined over the squamous part of the temporal bone, and the bone of the temporal fossa removed forwards, backwards and downwards. The dura is then opened, any branches of the middle meningeal artery being secured and ligatured. A drain of rubber tissue, or one-half of a split tube, should be inserted along the floor of the middle fossa of the skull between the dura and the brain. The dura is left widely open. The drain should be left in for forty-eight hours or longer as the case demands. The scalp flap is sutured into place by interrupted silkworm-gut sutures.

HISTOPATHOLOGICAL CHANGES FOLLOWING MALARIAL TREATMENT OF GENERAL PARALYSIS.[1]

BY RICHARD B. WILSON, M.D.
Atlanta, Ga.

THE unspecific treatment of general paralysis by the inoculation of malaria, initiated by Wagner-Jaurregg in the Vienna clinic, has justly led to renewed hopefulness in the combating of this disease. The very widespread adoption of this method, and the equally widespread favourable clinical results, give adequate attestation to this. That there are some disadvantages is well known, but certainly they are insignificant in comparison with the benefits derived.

At the moment the problem of greatest importance unquestionably is: What changes, following the introduction of the malarial parasite, take place in the organism that can bring about such improvement? To understand this obviously means considerable progress in the treatment, whether in the more effective employment of this method or of some other measure.

The first studies of this nature were reported in 1923 by Sträussler and Koskinas [36] on material from the Vienna Clinic. They presented the histological findings in seven cases. In four cases, in which the patients died during or directly after the treatment, the infiltration and proliferative changes in the vessels and glia were the most marked; the meninges were strongly infiltrated, macrophages being unusually numerous; the cortical blood-vessels likewise showed considerable infiltration, the infiltrative elements breaking into the nervous tissue itself in one case, and there was marked capillary and glial proliferation. On the other hand, in the three patients dying in remission there was surprisingly little change; the cortical architecture did not appear greatly disturbed, infiltration was very slight and the glia very little proliferated. They concluded that malaria leads to an increased intensity of inflammation, and that all defensive mechanisms of the central nervous system are

[1] From the Anatomical Laboratory (Professor Dr. A. Jakob) of the University Psychiatric Clinic, Hamburg-Friedrichsberg (Director Professor Dr. Weygandt).

mobilized against the noxus of the syphilitic disease. If the outcome is favourable then there is a recession of inflammation and the degenerative component of the paralytic process comes to a standstill—the picture of "stationary paralysis."

In 1925 the same authors [37] discussed the histopathological findings in thirty-one additional cases and extended their conception of the process to include a qualitative change, suggesting that the malarial treatment not only causes an increase in the intensity of the inflammatory reaction, but that the characteristic unspecific diffuse and malignant inflammation of general paralysis (Jakob [15]) is at least partially replaced by granulomata, a more specific and benign form of inflammation. This would indicate a favourable change in the reactive ability of the body.

In 1925 Kirschbaum [20] published his findings in twenty-two cases. In those terminating during and within two weeks after treatment he found, for the most part, moderately severe general paralytic changes, though in two there was very severe infiltration and in three very slight. In those terminating after a month the infiltration was slight. In a patient dying in a remission the state corresponded to "stationary paralysis." No convincing evidence was found of a change in character of the reaction. In only two cases were miliary gummata present.

In 1926 Gurewitsch [6] reported on twelve cases. In four patients, dying within three weeks after treatment, the changes were typical of general paralysis, and were of the severest degree. In the other eight, dying from three weeks to eight months, the changes were only moderately severe so far as the cortex was concerned, but in three there was marked infiltration of the striatum.

Among the cases examined by Nakamura (27) in 1926 are two of general paralysis which died during treatment and sixteen days after treatment respectively. In the first the paralytic changes were very severe, in the second of moderate severity. In general he was impressed by the prominence of lymphocytes and by the glial proliferation.

The findings in fifteen cases by Freeman [5] in 1927 were much the same as those of Sträussler and Koskinas. In cases examined within a few weeks of the first rigor he found a striking exaggeration of the usual paretic process, and was particularly impressed by the prominence of mesodermal proliferation. Later the picture gradually approaches the normal.

In contrast with practically all earlier findings are those of

Lehoczky [23] in 1927. He reported eleven cases treated with milk or malaria, or with a combination of the two. Of the six patients treated with malaria alone, one developed no fever and so must be excluded. One patient died fourteen days after treatment, the others during treatment. In only one case did he find intense infiltration of the cortical vessels, which in areas showed a very strong mesodermal proliferation. Another case showed similar changes confined to the left putamen. The remaining cases presented merely mild paretic changes. He thus believes that the favourable influence of malaria cannot be explained through an exaggeration of the inflammatory reaction as concluded by Sträussler and Koskinas, but rather that it causes a decrease of inflammation. He also found no evidence in support of Nakamura's claim of a change in quality, a relative increase of lymphocytes.

That some histological change takes place in the brain following inoculation by malaria seems beyond doubt, as judged by these reports, but as to the real nature of this change there is some lack of accord. Nor is it surprising that one should find considerable inconsistency in the histological picture. It is common knowledge how much at variance different cases of untreated paresis may be, and yet each possesses certain features which, when taken together, almost invariably permit a diagnosis to be made. However difficult, or even impossible, it may be to determine accurately from a few cases just what alterations may be due to the malarial treatment, it is not too much to presume that with the gradual accumulation of material certain features may become impressive by virtue of their constancy or their frequency. It is possible thus that the forty-seven cases of this report may offer some further evidence as to the nature of this process.

To follow such alterations through the various phases seemed possible only by grouping the cases according to the interval between treatment and death, and by constructing the largest possible groups so that the variations to be expected in the different cases might not obscure such features they might have in common. The following report attempts no detailed description of all the findings, but rather seeks to bring out the most characteristic changes at different intervals after treatment so that the process may be followed through its successive stages.

First, I shall consider only the thirty-eight cases that have run a clinical course fairly typical of paresis and in which the diagnosis could be verified histologically. For the above-mentioned reasons I shall describe these cases, all treated with tertian malaria, except where indicated, as follows:—

(1) 7 cases, death during treatment.
(2) 6 cases, death four to fourteen days after treatment (one patient inoculated with tropical malaria).
(3) 3 cases, death three to six weeks after treatment.
(4) 5 cases, death three to five months after treatment.
(5) 4 cases, death six to nine months after treatment (one patient inoculated with quartan malaria).
(6) 10 cases, death one to two and a half years after treatment (one patient inoculated with tropical malaria).
(7) 3 cases, death three to five years after treatment.

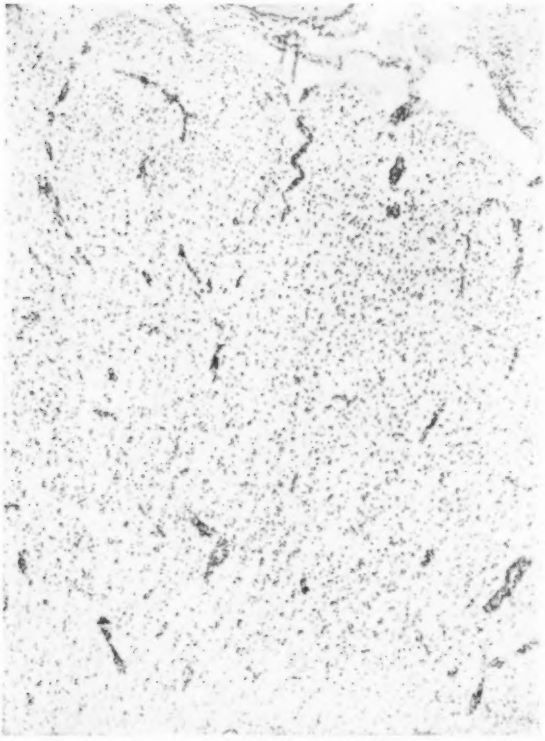

FIG. 1.—Nissl stain. Agranular frontal area. During treatment. Showing the strong and very diffuse infiltration characteristic of this period.

Group I.—SEVEN CASES TERMINATING DURING TREATMENT.

Clinical.—One patient, after having three typical rises of temperature, developed a step-like rise of fever lasting until death from "heart failure" three

days later. Four patients had eight, the other two eleven, rises of temperature. One patient developed pneumonia after the eighth elevation of temperature, and died the same day. The other patients died of "heart failure."

Histological.—The meninges are rather strongly infiltrated with plasma cells and lymphocytes, with a considerable predominance of the latter. There are also numerous mononuclear cells with varying amounts of cytoplasm in which one often sees small vacuoles and pigmented granules. These cells may be regarded as macrophages.

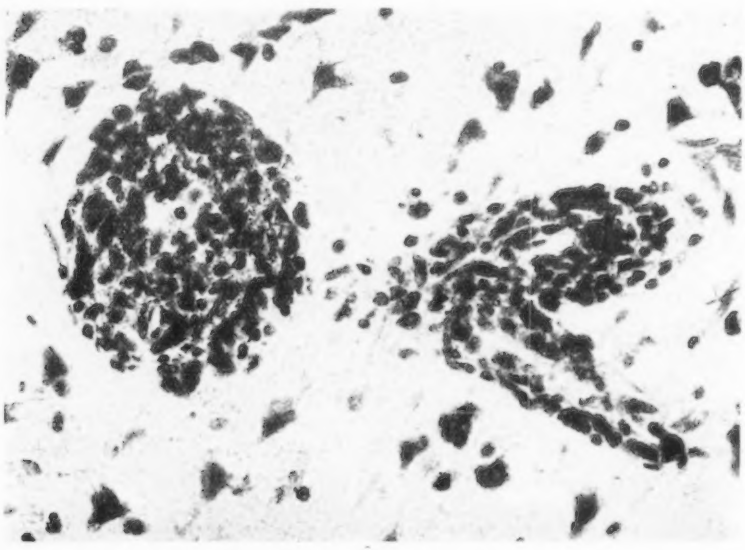

FIG. 2.—Nissl stain. During treatment. The more unusual findings of this period vessels with considerable mesodermal proliferation.

The cortex shows a quite typical histological picture of paresis, but the reaction is rather more intense than that found in the average case (fig. 1). The infiltration is very diffuse. Practically every vessel, large and small, has its mantle of plasma cells and lymphocytes with, as is usual, predominance of the former. In some instances the cells have broken the confines of the adventitial spaces and lie free in the tissue.

No impressively strong mesenchymal reaction is present, but in occasional vessels the mesenchymal tissue is somewhat more proliferated than usual (fig. 2), or a very thick ring of infiltration composed almost exclusively of lymphocytes may be found. At times there is considerable narrowing or even closure of the lumen of the vessels, or, rarely, even small inflammatory foci near them (fig. 3). Such exceptional findings, however, can scarcely be regarded as a real qualitative change in the reaction.

The macroglia is greatly proliferated, possessing large nuclei rich in chromatin and an increase of protoplasm. The microglia is even more proliferated, the nucleus being long and rod-shaped, as is usually found in paresis. The iron reaction in both the walls of the blood-vessels and in the microglia is very strong. The architecture of the cortex is markedly disturbed, so that it is often difficult to recognize the several layers. The changes in all groups of ganglion cells are so nearly alike that there appears no reason for discussing them

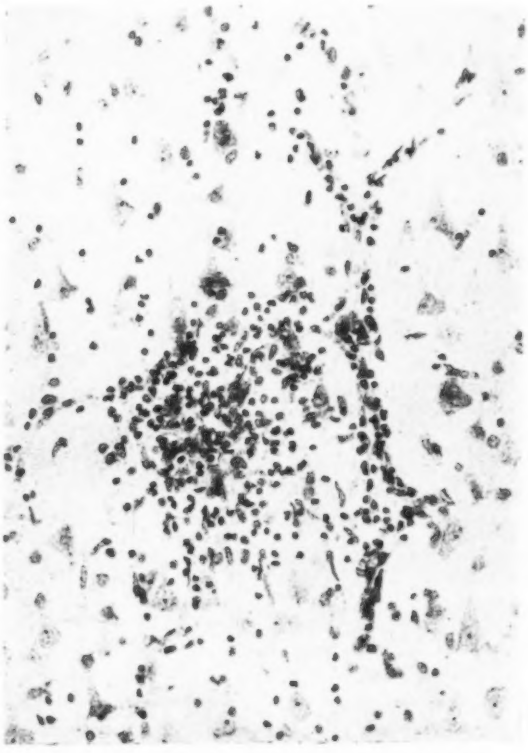

FIG. 3.—Nissl stain. During treatment. An inflammatory focus near a small vessel, such as may rarely be found.

further, much less for giving separate descriptions in the different cases, or even in the several groups. Even the cases in which there is considerable restoration of the arrangement of the cortical layers and of the nerve cells also show severe alterations in the ganglion cells.

Fig. 1 represents the type of reaction characteristic of the cases dying during

treatment. This may be summarized as an increase in intensity of the usual general paralytic reaction. No spirochætes were found.

Other findings which do not characterize the cases of this period, but which may deserve mention for the sake of more complete description, can be briefly summarized.

The degree of meningeal thickening varies considerably in the different cases, not only at this period but in all cases. There is, however, no evidence that it is influenced by the treatment, and so it may be left out of further consideration. In addition to the meningeal infiltration already mentioned,

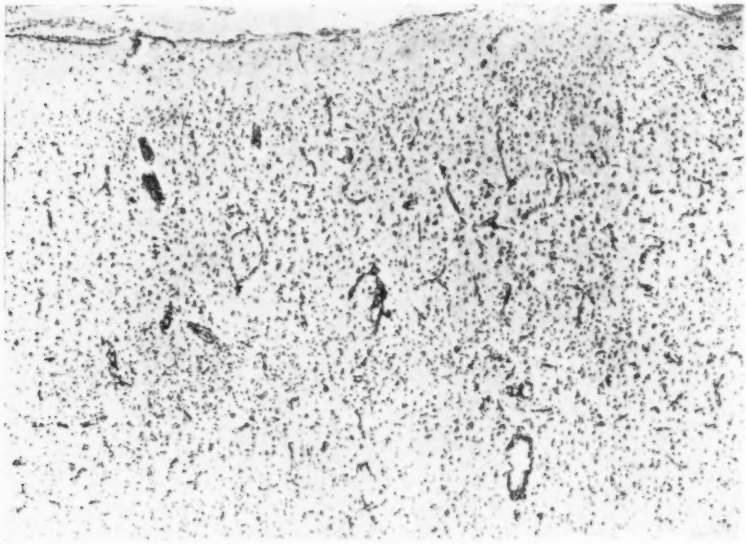

FIG. 4.—Nissl stain. Temporal lobe; seven days after treatment. The intense diffuse infiltration is still to be seen.

there are, in one case, great numbers of mast cells and degenerated plasma cells (mulberry forms). In another case many Russell's bodies are present.

In some cases degenerative changes of the walls of the blood-vessels are found. In one case, for example, an occasional vessel shows a moderate degree of intimal thickening and proliferation of the endothelial cells. In another, one fairly large cortical blood-vessel was found with thickened intima and splitting of the internal elastic membrane. Here and there are vessels with hyaline changes or deposits of chalk. The occasional thick perivascular lymphocytic rings, the less common vessels with considerable mesodermal proliferation and the rare inflammatory foci lying near the blood-vessels, have already been mentioned (figs. 2 and 3). In one case considerable blood-pigment is present in the perivascular spaces.

In some cases glial rosettes are found in the white substance, which unquestionably indicate degeneration of fibres. Jakob [14], in his study of secondary degeneration, has described in detail the relationship of glial rosettes to fibre degeneration. Such findings, however, so far as my observations go, bear no relation to the malarial treatment.

Group II.—Six Cases, Four to Fourteen Days after Treatment.

Clinical.—One patient had a few slight convulsive attacks following treatment and later developed pneumonia which led to death. The others became

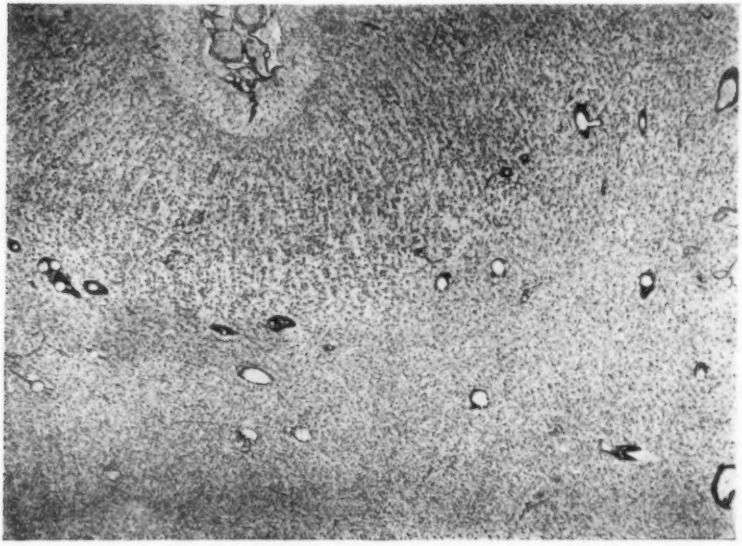

Fig. 5.—Nissl stain. Granular frontal area; three weeks after treatment. A case showing the most marked accumulation of infiltration on the small blood-vessels. This indicates the recession of the diffuseness; the capillaries are less strongly infiltrated.

increasingly demented, dying usually in a state of marasmus, some with decubitus. One patient had only three rises of temperature, the others from six to twelve.

Histological.—In this period the changes are even more severe. The meningeal infiltration remains practically the same as during treatment except for a rather striking increase of macrophages. In the cortex the perivascular infiltration has become yet greater. Here, as in the first group, plasma cells predominate and the infiltration is still very diffuse, but it differs in that somewhat thicker cell rings on the venules and arterioles are more frequent (fig. 4). The macroglia is more strongly proliferated, the microglia to practically the

same degree as in the previous groups. The iron content of the blood-vessel walls, as well as of the microglia, manifests some further increase. The disturbance of cortical architecture remains essentially the same.

In one of these cases I was able to find spirochætes, but otherwise this case did not differ from the others of the group except for the presence of a great number of Russell's bodies ("colloidal plasma cells").

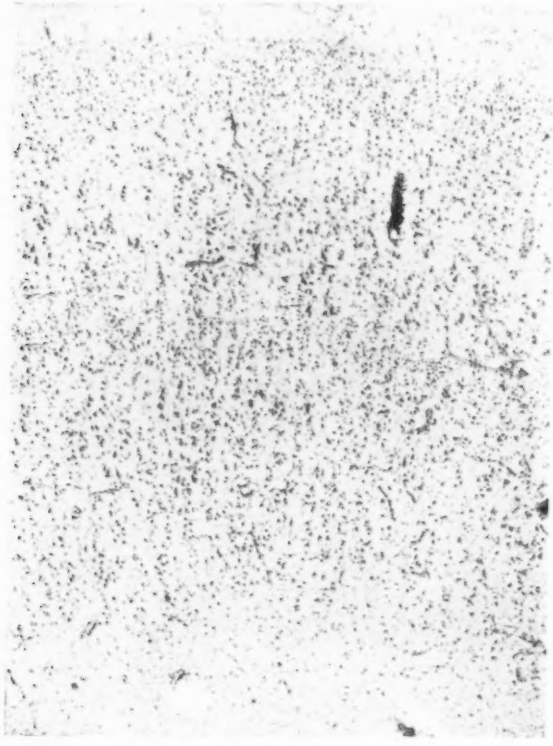

FIG. 6.—Nissl stain. Granular frontal area; six weeks after treatment. A case showing the least accumulation of infiltration on the small blood-vessels. This and fig. 5 represent thus two extremes, the other case falls in between.

Group III.—THREE CASES, DYING THREE TO SIX WEEKS AFTER TREATMENT.

Clinical.—One patient, without showing improvement, developed a bronchitis and cyanosis, increasing until death. The second had hallucinations, was excited, then gradually became weaker, developed a phlegmon and died in a

state of marasmus. The third became somewhat maniacal and excited, gradually grew weaker and died of circulatory failure. All cases had six to ten elevations of temperature.

Histological.—In this period the severity of the histological changes reaches its maximum, but after this stage gradually diminishes.

FIG. 7.—Nissl stain. Granular frontal area; three months after treatment. The diminution of infiltration and the improved appearance of the cortical architecture are evident.

The intensity of the meningeal infiltration is essentially the same, but has undergone a change in character, in that the plasma cells are now quite as numerous as the lymphocytes. The macrophages are considerably reduced, The perivascular infiltration in the cortex is even greater, but its character has changed in that the capillaries are somewhat less strongly infiltrated, while thicker accumulations on the arterioles and the venules tend to characterize the picture (figs. 5 and 6). The infiltration is becoming less diffuse than in the cases dying during treatment.

The macroglia, especially strongly proliferated between four to fourteen days after treatment, is now even less proliferated than during treatment, while the microglia at this time is enormously increased. Of all periods none gives such a strong iron reaction or shows such a proliferation of microglia.

The cortical architecture is perhaps somewhat less disturbed than in the earlier cases. No spirochætes were found.

FIG. 8.—Nissl stain. Granular frontal area; nine months after treatment. The cortex shows continued restoration.

Group IV.—FIVE CASES, DYING THREE TO FIVE MONTHS AFTER TREATMENT.

Clinical.—Three of these cases became steadily worse, both physically and mentally: one terminated in pneumonia, the other two were excited, one dying suddenly in a bath, the other as a result of a broken rib. All cases had six to eleven elevations of temperature.

Histological.—In this period one sees fairly marked regression of practically all changes. The infiltration of the meninges is much less; particularly marked is the decrease of plasma cells. The cortical perivascular infiltration has become considerably reduced, especially around the capillaries. It is confined chiefly to the arterioles and venules, which show here and there small accumulations of lymphocytes and plasma cells in the adventitial spaces.

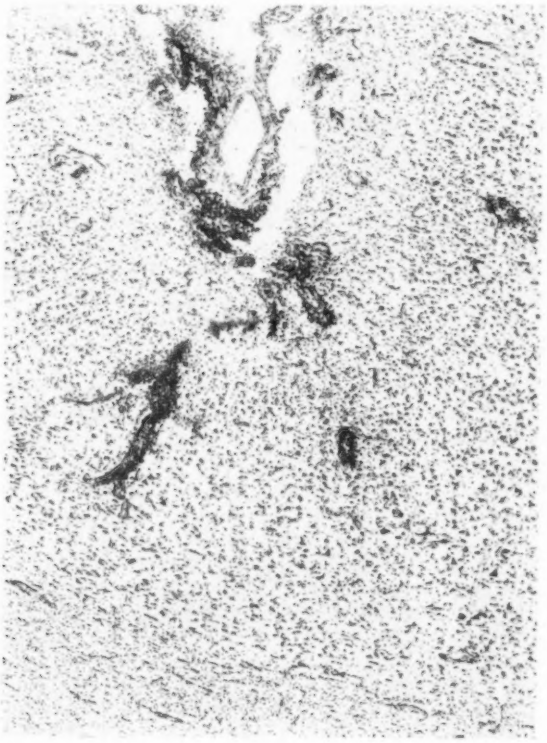

FIG. 9.—Nissl stain. Intermedial frontal area; six months after treatment. Inflammatory focus of massively infiltrated vessels, the cells breaking through into the nervous substance. In this case spirochætes were found.

The proliferation of the glia has become considerably less. The most striking improvements of all are the diminution in the iron content of the blood-vessels and microglia, the decrease in the proliferation of the microglia and the reduction of plasma cells in the meninges. The architecture of the cortex now, for the first time, has a more normal appearance.

Fig. 7 represents the average appearance of this group, and in comparing

it with the previous micrographs one is able to recognize a diminution of infiltration and a more orderly arrangement of the nerve-cells. No spirochætes were found.

Group V.—Four Cases, Dying Six to Nine Months after Treatment.

Clinical.—These cases all presented very much the same clinical course: gradual physical and mental deterioration without improvement: restlessness or severe excited states; one patient died in such a state after having had hallucinations earlier. The cases had nine to ten rises of temperature.

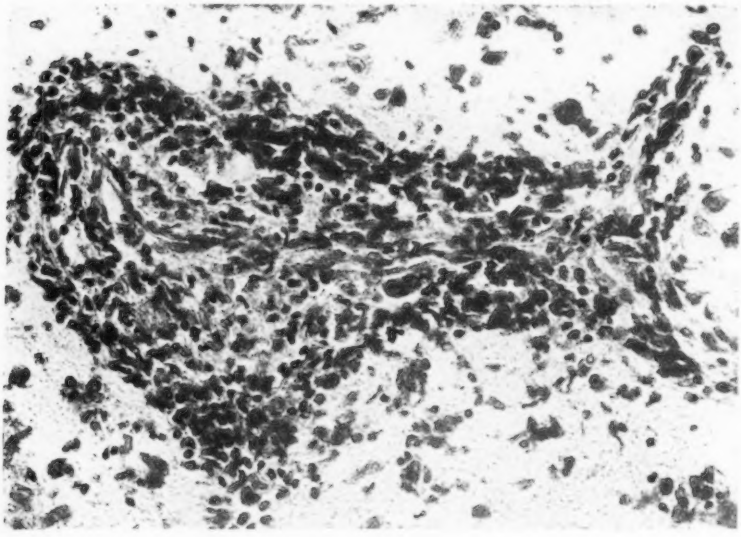

Fig. 10.—Nissl stain. Same case as fig. 9. The vessel is represented by a dense strongly infiltrated mesenchymatous mesh with obliteration of the lumen. (Unorganized granuloma, *Jakob.*)

Histological.—At this time a second point of significance is reached. Either the improvement continues still further, or a severe and rather unusual inflammatory reaction is to be seen. In three cases there is a still further regression of practically all histological changes. The infiltration has diminished further, but remains predominantly plasma cell in type. The iron content of the walls of the blood-vessels and of the microglia has undergone further reduction. There is still less proliferation of the microglia. The cortical architecture, too, shows considerable improvement (fig. 8). In these three cases I was unable to find any spirochætes.

In the fourth case the changes are more severe than in any of the previously described twenty-four cases, and differ also in character. In the former cases the infiltration was fairly uniform; here it is most irregular in intensity in different areas (*herdförmig*). Whereas in most regions of the cortex one finds only a few plasma cells and lymphocytes along the capillaries and numerous small vessels with rings of infiltration consisting chiefly of lymphocytes, there are numerous areas of intense infiltration in which there is marked proliferation of the walls of the larger vessels, which often has led to considerable narrowing of the lumen, and in this mesenchymal network are embedded many infiltrating cells, some of which are plasma cells, but most lymphocytes. The infiltration no longer remains within the confines of the membrana limitans but has broken through into the nervous tissue itself (figs. 9 and 10). The capillaries and smaller vessels are most severely infiltrated and numerous lymphocytes are scattered throughout the adjacent nervous tissue. Rod cells are extremely abundant in these areas and are more numerous than in any of the cases thus far considered. The macroglia cells, too, are present in great numbers and there is a considerable increase of their protoplasm so that the cell bodies appear round and swollen. The blood-vessel walls and microglia give an unusually strong iron reaction. Fig. 9 shows clearly the severe disturbance in the architecture of the cortex. In this case spirochætes were found.

I wish to emphasize the fact that, after the beginning of restitution, spirochætes were not found in any case until six months after treatment. In the above case, the first in which they were found after this interval, the histological changes are of a very different character from any found in the previously described cases (twenty-four), but resemble closely the changes found in the relapsing cases of the following group.

Group VI.—Ten Cases, Dying One to Two-and-a-half Years after Treatment.

Because of the clinical as well as the histological complexity of this group, it seems advisable to give a short summary of the clinical course of each case, and for the sake of better comparison I shall consider first those with insignificant histological findings, then the cases with severe changes.

(A) *Five Cases with Slight Histological Changes.*

Case 26 (Sau.).—Admitted May 14, 1924. The patient was excited, euphoric and expansive. Blood Wassermann + + + + ; C.S.F. Wassermann 3-4-4 [1] ; cells, 111 ; N.A. + ; Wb. + + + ; mastic, very strong paretic curve.

[1] C.S.F. Wassermann = 3-4-4 according to amount of C.S.F. used, i.e., 0·2-0·5-1·0. N.A. = Nonne-Apelt test for globulin. Wb. = Weichbrodt's reaction for globulin. Mastic (normomastic technique) is indicated as very strong paretic curve (7-9-12-12-12-12-11-9-6-5-5-4-4-3), strong, weak, very weak. lues cerebri or typical lues cerebri curve (3-4-6-8-7-6-5-4-4-3-3-3-2-2).

June 10, 1924: Inoculated with tertian malaria, ten rises of temperature.

July 8, 1924: Blood Wassermann ++++; C.S.F. Wassermann 4-4-4; cells, 4; N.A. +; Wb. +; mastic: strong paretic curve.

August 26, 1924: The patient was quieter and mentally clearer. Blood Wassermann ++++; C.S.F. Wassermann 1-4-4; cells, 6; N.A. +; mastic: lues cerebri curve.

January, 1925: Further mental deterioration became evident, associated with hallucinations. Later the deterioration became more rapid, the patient became dyspnœic, increasingly œdematous, finally stuporous, and died July 22, 1925.

Case 27 (Mut.).—Admitted January 10, 1923. The patient was expansive, and exhibited considerable defect of memory and speech. Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells, 92; N.A. ++; Wb. +++.

January 31, 1923: C.S.F. Wassermann 3-3-3; cells, 28; N.A. ++; Wb. +++.

February 3, 1923: Inoculated with tertian malaria; seven rises of temperature.

March 2, 1923: The patient was little changed, continuing euphoric, expansive and profane. Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells, 21; N.A. ++; Wb., slightly opalescent.

April 5, 1923: Blood Wassermann +++; C.S.F. Wassermann 1-3-3; cells, 14; N.A. opalescent; Wb. ±.

May 5, 1923: Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells, 14; N.A. opalescent; Wb. ±.

June, 1923: The patient showed some improvement, though he continued expansive.

July, 1923: Improvement was such that the patient, no longer expressing expansive ideas, was able to play cards. Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells, 9; N.A. ±; Wb. +.

September, 1923: Tube feeding became necessary and deterioration continued. Died January 16, 1924.

Case 28 (Fan.).—Admitted July 28, 1923. The patient was confused, had hallucinations, and exhibited defects in speech and in writing. Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells, 77; N.A. opalescent, Wb. ++.

August 1, 1923: Inoculated with tertian malaria: fourteen rises of temperature.

September 10, 1923: He was manifesting increasing dementia and had several convulsive attacks. Blood Wassermann ++; C.S.F. Wassermann 0-2-3; cells, 4; N.A. ±; Wb. ++; mastic: strong paretic curve.

October 2, 1923: No improvement. Blood Wassermann +++; C.S.F. Wassermann 1-3-3; cells, 5; mastic: very weak paretic curve.

January, 1924: The patient developed progressive dementia. Blood Wassermann +++; C.S.F. Wassermann 2-3-3; cells, 2; N.A. opalescent, Wb. +; mastic strong paretic curve. Continuing downhill the patient became emaciated and developed decubitus. Died November 20, 1924.

Case 29 (Ref.).—Admitted September 22, 1923. The patient was at times depressed, at times expansive. Blood Wassermann negative (Stern + + +); C.S.F. Wassermann 1-1-3; cells 15; N.A. opalescent; Wb. +.

October 2, 1923: Inoculated with tropical malaria; four rises of temperature.

November 15, 1923: No improvement. Blood Wassermann negative; C.S.F. Wassermann 0-1-3; cells 4; N.A. trace opalescence; Wb., opalescent; mastic: strong paretic curve.

1924: His condition became slowly worse and there were occasional convulsive attacks.

January, 1925: Blood Wassermann negative (Stern + +); C.S.F. Wassermann 1-3-3; cells 18; N.A. ±; mastic: very weak paretic curve. The patient became increasingly indifferent and demented until death from heart failure, April 15, 1925.

Case 30 (Hed.).—Admitted October 30, 1922. The patient was confused and showed considerable mental deterioration. C.S.F. Wassermann 2-3-3; mastic: strong paretic curve.

November 11, 1922: Inoculated with tertian malaria; seven rises of temperature.

January 23, 1923: The patient had been able to work fairly well about the hospital and had improved sufficiently to be discharged.

February 18, 1924: Re-admitted because of an attack of unconsciousness a few days before. He had previously been well. Blood Wassermann negative; C.F.S. Wassermann 0-2-3; cells 3; N.A. trace of opalescence; Wb. opalescent; mastic: very weak paretic curve. He was depressed and indifferent, but improved rapidly and was discharged again March 31, 1924.

November 15, 1924: Re-admitted because of depression and an attempt at suicide. He was restless and noisy. His anæmia, marked on admission, became steadily worse. Death, November 24, 1924.

(B) Five Cases with Severe Histological Changes.

Case 31 (Rud.).—On admission, November 20, 1924, the patient was euphoric and indifferent. Blood Wassermann + + + +; C.S.F. Wassermann 0-1-3; cells 22; N.A. opalescent; Wb. +; mastic: very strong paretic curve.

December 3, 1924: Inoculated with tertian malaria; seven rises of temperature.

April, 1925: The patient had become gradually worse, continuing euphoric and wholly without insight. Blood Wassermann + + + +; C.S.F. Wassermann 0-0-2; cells 69; N.A. +; mastic: strong paretic curve.

September, 1925: Blood Wassermann + + + +; C.S.F. Wassermann 4-4-4; cells 64; mastic: very strong paretic curve. There was gradual deterioration until death by suffocation while eating, November 13, 1925.

Case 32 (Jac.).—On admission, June 14, 1924, the patient was considerably demented, indifferent and profane. Blood Wassermann + + +; C.S.F. Wassermann 2-4-4; mastic: weak paretic curve.

July 10, 1924: Inoculated with tertian malaria; seven rises of temperature.

November, 1924: No improvement. Blood Wassermann + + + + ; C.S.F. Wassermann 2-4-4; cells 10: N.A. trace opalescence; Wb. opalescent; mastic: weak paretic curve.

February, 1925: The patient had hallucinations, was confused and indifferent.

March, 1925: He was euphoric and indifferent. He became gradually emaciated. Died, April 11, 1926.

Case 33 (Rat.).—On admission, January 15, 1923, the patient was markedly demented and showed defects in speech and writing. Blood Wassermann + + +; C.S.F. Wassermann 3-3-3; cells 260; N.A. +; Wb. + +.

February 1, 1923: Inoculated with tertian malaria. Nine rises of temperature.

March 1, 1923: Blood Wassermann + + + ; C.S.F. Wassermann 3-3-3; cells 15; N.A. + + ; Wb. + +.

July, 1923: Blood Wassermann + + (Stern +); C.S.F. Wassermann 3-3-3; cells 5; N.A. ± ; Wb. + +. The patient had improved and was discharged in a fairly good remission.

February, 1924: Re-admitted, more confused and indifferent. Blood Wassermann + + + + ; C.S.F. Wassermann 4-4-4; cells 11; N.A. +; Wb. + +: mastic: strong paretic curve. After improving slightly for a time he showed more rapid mental deterioration, and towards the end developed decubitus. He died November 23, 1925.

Case 34 (Rev.).—On admission, September 7, 1923, the patient was confused, indifferent, demented, and at times excited. Within the first few days he had three convulsive attacks. Blood Wassermann + + + ; C.F.S. Wassermann 3-3-3; cells 516; N.A. +.

October 6, 1923: Inoculated with tertian malaria, and had typical rises of temperature—number unknown.

January 9, 1924: The patient showed no improvement, was very noisy, euphoric and restless. He was without insight and developed progressive dementia. Blood Wassermann + + + ; C.S.F. Wassermann 3-3-3; mastic: lues cerebri curve.

April, 1924: He had improved enough to work about the hospital, and to be discharged in August, 1924.

July, 1925: Re-admitted because of sudden loss of speech. He was indifferent and showed increased dementia. Blood Wassermann + + + + ; C.S.F. Wassermann 4-4-4; cells 390: N.A. ±: mastic: very strong paretic curve.

October, 1925: The patient continued downhill and had several convulsive attacks.

February, 1926: He was becoming progressively demented, very restless and noisy, and later increasingly emaciated until he died May, 1926.

Case 35 (Kei).—On admission June 23, 1923, the patient was confused and very irascible. Blood Wassermann + + + ; C.S.F. Wassermann 3-3-3; cells 11; mastic: strong paretic curve.

July 2, 1923: Inoculated with tertian malaria; eight rises of temperature.

August 24, 1923: Considerable improvement. C.S.F. Wassermann 3-3-3: cells 16; N.A. negative; Wb. +; mastic: typical lues cerebri curve.

November 23, 1923: She was discharged in a fairly good remission and was able to carry on housework and conduct a store.

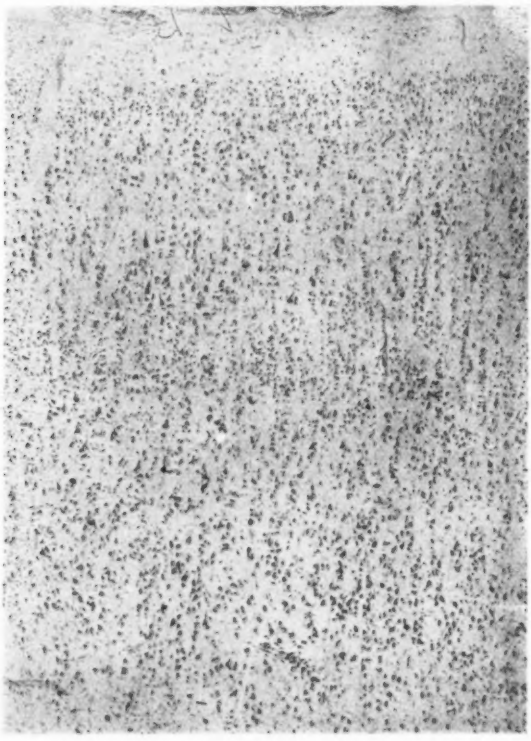

FIG. 11.—*Case* Sau. Nissl stain. Superior parietal area; one year after treatment. Except for evident loss of ganglion cells the cortex presents a fairly good appearance.

July, 1924: Re-admitted. She was confused, irascible and without insight. C.S.F. Wassermann 3-3-3; cells 90; N.A. +. She became progressively demented and had a convulsive seizure on the day before death, October 10, 1924.

Histological.—The first five cases (Group A) present very much the same histological picture as the three cases of the preceding group (six to nine months). The changes are slight: the meningeal infiltration is of only a mild degree, but there is a fairly marked relative increase of macrophages.

Of interest is the further improvement in the appearance of the cortical architecture (fig. 11). A fairly marked loss of ganglion cells is obvious at once (numerous small areas devoid of cells are evident in the photomicrographs), which clearly indicates that considerable destruction has already been effected. Nor can one speak of normal ganglion cells, for there is a great variety of changes to be seen in them. Nevertheless the orderliness of the nerve cells and the much neater arrangement of their layers, as compared with those cases terminating early after treatment and with the usual cases of general paralysis, is at least impressive. This in itself does not speak for a very active destructive or degenerative process.

The infiltration of the cortical blood-vessels is also very slight, only a few lymphocytes and plasma cells being found here and there on the smaller vessels, more rarely still on the capillaries.

It is surprising, in view of these findings, that the microglia is more strongly proliferated than in the preceding period. The iron reaction in the blood-vessels and microglia has become stronger.

In none of these cases was I able to find spirochætes.

In striking contrast to the findings in the first five cases are those of the following five of the same period, one to two-and-a-half years after treatment (Group B). The latter present very much the same reaction as the case (Tim) of six to nine months (fig. 10) and also show some tendency towards a more focal distribution of inflammation, with variations of the picture in different cases. For example, in the case (Rev.) there are only a few lymphocytes and plasma cells along the capillaries and in some areas occasional, in other areas many, larger vessels with thick infiltration rings, in most of which plasma cells predominate, though in some lymphocytes are in the majority. In the case (Rat.) the capillaries are as a rule rather strongly infiltrated with plasma cells, but in some places the perivascular infiltration forms thick rings in which occasionally the cells show a tendency to be arranged in layers. In the other three cases the capillaries show from a very slight to a moderate degree of infiltration; the small vessels, in some areas, present all degrees of mesenchymal proliferation, with increasing organization of the infiltrating elements to the formation of miliary gummata, as in case (Rud.) (figs. 12 and 14). The iron reaction in these cases is very marked, in fact greater than in any group of cases except those dying in three to six weeks. There is the same moderate degree of proliferation of the microglia and the macroglia as in the preceding five cases. The disturbance of the cortical parenchyma is of a moderate severity, and is more pronounced where the inflammatory foci are situated. Whereas in the first five cases of this period with only slight changes no spirochætes were found, spirochætes were found in four of the last five.

Group VII.—Three Cases, Three to Five Years after Treatment.

These three cases present rather varied histological pictures, and so it seems advisable to give briefly the more outstanding features of each case.

FIG. 12.—*Case* Rud. Nissl stain. Eleven months after treatment. Inflammatory focus. In the thickened walls of the larger vessel the infiltration is organized in layers.

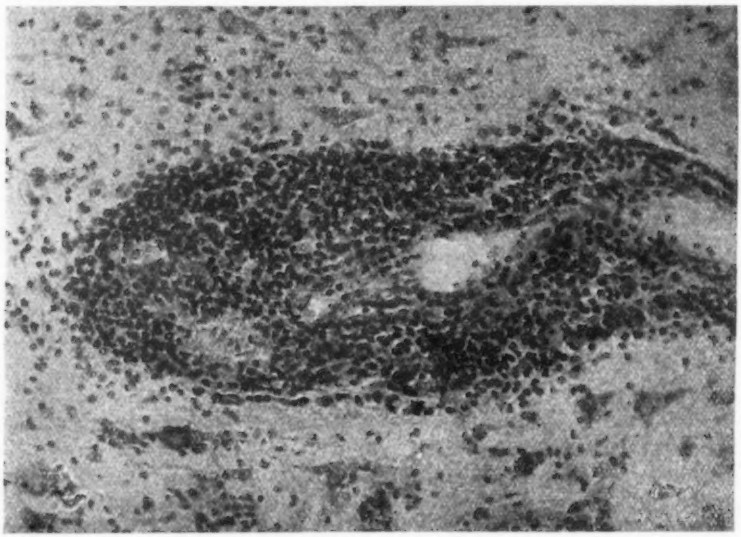

FIG. 13.—Nissl stain. Same case as fig. 12. The massively infiltrated mesenchymal mass forms a considerable excrescence in the vessel wall. In the centre areas of paleness are evident.

Case 36 (Wie.).—Admitted September 6, 1921, with marked euphoria and considerable speech defect. Blood Wassermann + + + ; C.S.F. Wassermann 3-3-3 ; cells 15 ; N.A. + ; Wb. + ; mastic : weak paretic curve.

September 12, 1921 : Inoculated with tertian malaria ; eleven rises of temperature.

November 4, 1921 : He was quiet, able to help with the work, possessed insight into his condition and could be discharged November 21, 1921. At home he continued to improve.

July, 1922 : Readmitted because of convulsive attacks. He was at times apathetic, at times euphoric. C.S.F. Wassermann 3-3-3.

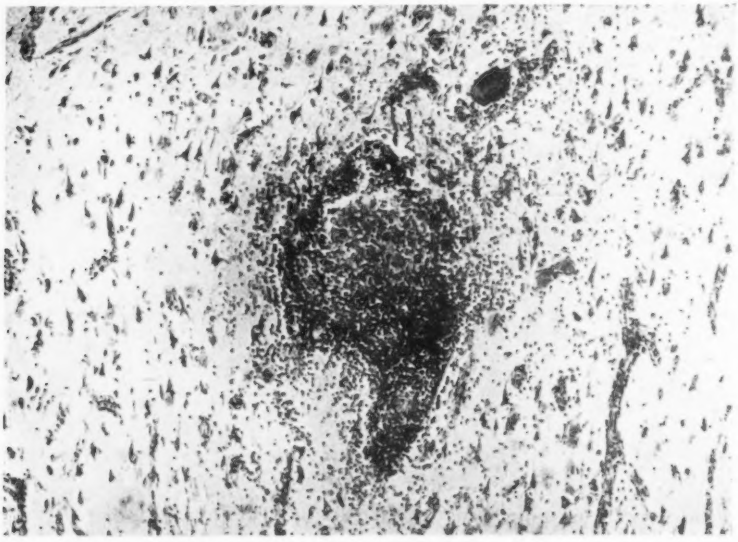

FIG. 14.—Nissl stain. Same case as fig. 12. Miliary gumma with necrosis and giant cells.

October, 1922 : No improvement. He had several convulsive attacks.

1923-24 : Dementia gradually increased, associated with occasional convulsive attacks. March, 1924 : Blood Wassermann ± ; C.S.F. Wassermann 3-3-3 ; cells 34 ; N.A. + ; mastic : very strong paretic curve.

January, 1925 : He was almost totally demented, and he died on February 2, 1925.

Histological.—The meninges are only slightly thickened. The infiltration is of a very mild degree, lymphocytes and plasma cells being equally numerous. Quite a number of mast cells are scattered throughout. The several cortical layers present very little disorder, though many ganglion cells have fallen out.

The cortical perivascular infiltration is that of a mild paretic type, with some proliferation of the microglia and a feeble iron reaction in the walls of the blood-vessels and in the microglia.

Case 37 (Bec. W.).—On admission, October 12, 1920, the patient was disoriented, demented and euphoric.

October 21, 1920: Inoculated with tertian malaria; two rises of temperature.

1921-23: Slowly increasing dementia, with occasional convulsive attacks.

September, 1924: Re-inoculated with tertian malaria, but no typical rises of temperature followed, though he ran a slightly febrile course for six days. Afterwards dementia became steadily more marked and he became more and more emaciated. He died in October, 1925.

Histological.—The parenchymatous changes as well as intensity of the inflammatory reactions are somewhat more severe than in the previous case. In three areas there is intense perivascular infiltration, with numerous cells breaking into the brain substance, and in two of these areas mesenchymal proliferation is marked. The iron reaction in this case is of a slight degree, the microglial proliferation fairly pronounced. Numerous mast cells are found in the meninges, fewer in the cortical perivascular spaces. No spirochætes were found.

Case 38 (Wul.).—On admission, October 10, 1922, the patient was demented and had disturbances of speech. Blood Wassermann + + +; C.S.F. Wassermann 3-3-3; cells 286; N.A. ±; Wb. + +.

October 20, 1922: Inoculated with tertian malaria; seven rises of temperature.

November, 1922: C.S.F. Wassermann 3-3-3; cells 41; N.A. ±; Wb. +; mastic: very strong paretic curve.

December, 1922: C.S.F. Wassermann 3-3-3: cells 35; N.A. +; Wb. + +.

January, 1923: Blood Wassermann + + +; C.S.F. Wassermann 3-3-3; cells 17; N.A. ±.

February, 1923: The patient had improved enough to help in the ward, but was euphoric. Blood Wassermann + + +; C.S.F. Wassermann 3-3-3; cells 11; N.A. opalescent: mastic: strong paretic curve.

March, 1923: Blood Wassermann + +; C.S.F. Wassermann 3-3-3; cells 14; N.A. ±.

April, 1923: Blood Wassermann + + +; C.S.F. Wassermann 2-3-3; cells 31; N.A. ±; Wb. + +; mastic: weak paretic curve.

February, 1924: The patient continued to help with the ward work, though his condition remained practically the same as the year before. Blood Wassermann, ±; C.F.S. Wassermann 3-3-3; cells, 25; N.A. opalescent; mastic: weak paretic curve.

June, 1924: The patient was working regularly in the garden, reading, playing cards, and quite orderly in his habits, though he continued slightly euphoric. Blood Wassermann + + + +; C.S.F. Wassermann 1-3-4; cells, 8; N.A. ±; Wb. ±; mastic: weak paretic curve.

May, 1925: The patient was no longer capable of working in the garden. He remained in bed quite indifferent and filthy in his habits. He died September, 1926.

Histological.—The meninges show a moderate degree of thickening and of inflammation. In the cortex there is marked architectural disturbance, and a considerable loss of ganglion cells. The perivascular infiltration is in all pre-

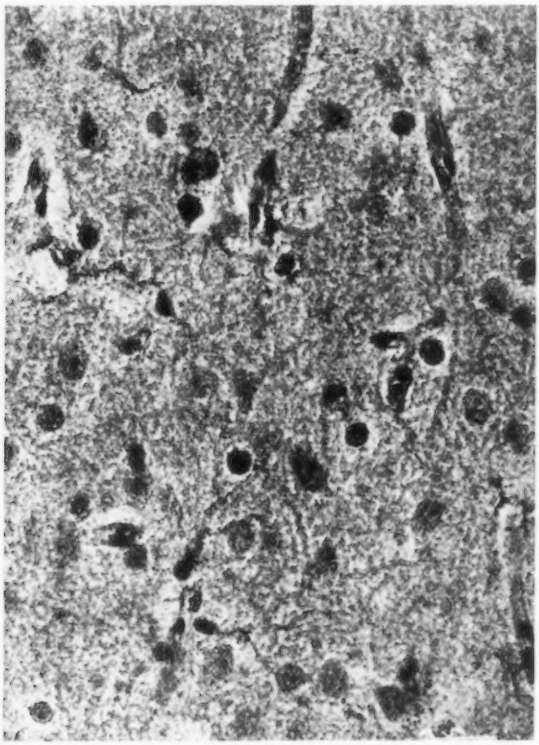

FIG. 15.—*Case* Mey. Hortega silver method. An area in which the microglia was found most strongly proliferated.

parations noticeable, and in many areas very pronounced. Many vessels have thickened walls, some so thickened as to obliterate almost completely the lumen. The thickened walls are a spongy mesenchymal net, the meshes of which are filled with infiltrating cells which frequently break into the nervous tissue. These correspond to the "unorganized granuloma" of Jakob. Occasionally pale areas are encountered in the centre of such a granu-

loma, and rarely a giant cell may be found adjoining it. This, no doubt, represents an early miliary gumma. The microglia is considerably proliferated and swollen macroglia cells are very numerous. There is an unusually strong iron reaction in the walls of the blood-vessels and in the microglia cells; the oligodendroglia and macroglia also contain a noticeable amount of iron. Spirochætes were found. This case thus corresponds rather closely to the

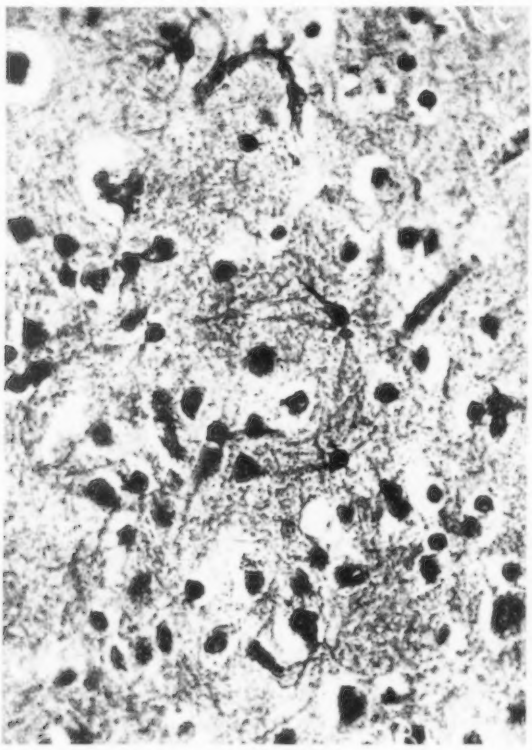

FIG. 16.—Case Mey. Cajal's gold chloride method. Condition where the macroglia was found most markedly proliferated.

five cases of the one to two-and-a-half years period, that showed such marked histological changes, and in 80 per cent. of which spirochætes were found.

The other two cases, in which there were far less marked changes, cannot be identified with any of the previously described groups. Both show typical paretic changes, the first of a very mild degree as judged by the severity of parenchymatous changes, the intensity of infiltration, the glial proliferation

and the iron reaction, while the second is of greater severity. Nevertheless, these two cases, in contrast with the above case in which spirochætes were found, resemble more closely those of the period one to two and a half years, in which no spirochætes could be discovered, and in which the histological changes were slight.

In connection with these cases, which were clinically and histologically general paresis, it may be of interest to consider the findings in a case dying during a remission.

Case 39 (Mey).—(Observed and treated by Professor Jakob.)

Clinical.—Female, aged 43, May 3, 1923. She had no knowledge of luetic infection. For one year there had been mental change, especially poor memory, sleeplessness, impaired judgment, periods of depression, negligence of household, intellectual deterioration and speech disturbance. Her pupils were irregular and reacted poorly to light. Blood Wassermann + + + ; C.S.F. Wassermann + + + + ; mastic: general paralytic curve.

May 8, 1923: Inoculated with malaria; first rise of temperature three days later: in all eight rises. Directly after the treatment the patient showed improvement, which continued until she was able to resume her social life and discharge fully her household duties. Death occurred in October, 1926, following operation for carcinoma of the stomach.

Histological.—The meninges are thickened to a moderate degree and slightly infiltrated, chiefly with lymphocytes, in fact in many areas plasma cells are extremely rare. The cortex shows little disturbance. The ganglion cells and the different layers present a very orderly arrangement. Numerous small areas devoid of ganglion cells suggest, however, that considerable destruction has already taken place. Here and there are arterioles with thickened fibrous walls. In some sections a few plasma cells and lymphocytes are encountered in the perivascular spaces, but in most they are rare. The microglia and macroglia are practically normal. Figs. 15 and 16 were taken from areas where they were richest in protoplasmic processes. The iron reaction in the walls of the blood-vessels is moderately strong, and a considerable amount of iron is found in the macroglia but much less in the oligodendroglia. Practically no iron could be found in the microglia. No spirochætes were seen. This case shows clearly how far restitution may go.

Having pointed out the more striking histological change at various intervals after treatment by malaria, I can now review my findings, in conjunction with those of other investigators, in an effort to present a picture of the series of histological reactions most likely to occur in the brain following inoculation with the malarial parasite.

In order to facilitate comparison, I have attempted in each block of tissue to estimate the intensity of the various reactions, and have designated this as +, + +, + + +, and + + + +. On this basis, it was possible to construct a chart showing the severity of the changes during

treatment and at different periods after the treatment (fig. 17). In this chart I have not included the six cases in which there was a recrudescence of inflammation, since this differed in character to such a

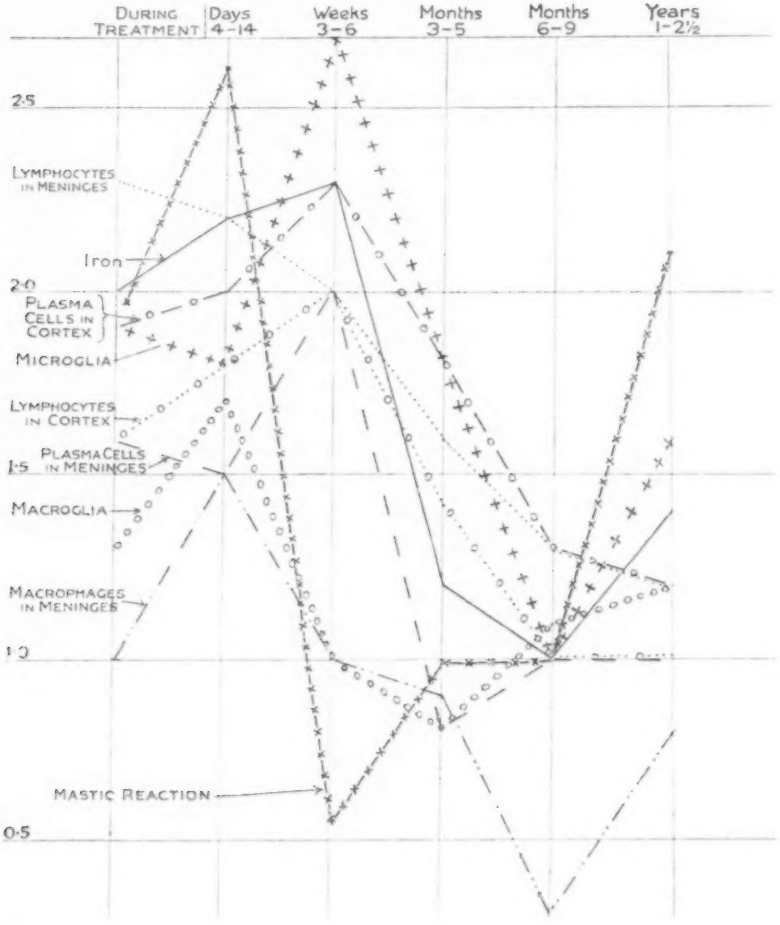

Fig. 17.—Chart indicating the intensity of the various reactions at successive intervals after treatment.

degree that the intensity could not be estimated by the same standards employed for the other cases.

Roughly, three divisions become at once possible. *First, a period*

of exacerbation of all changes, commencing during treatment and persisting until from three to six weeks after treatment. *Second*, following the period of exacerbation, a *period of restoration*, which may continue uninterrupted for years (in about half of my cases). *Third* (in the other half of my cases), there may take place, any time after six months, a new flare up in the histological process, a *period of recrudescence*.

Period of Exacerbation (Sixteen Cases).

During treatment and up to three to six weeks after treatment, the typical picture of general paralysis in its severest form is found. This includes derangement of the cortical layers and of the nerve-cells; meningeal and cortical perivascular infiltration; macroglial and microglial proliferation, and a strong iron reaction in the walls of the blood-vessel and in the microglia.

The lymphocytes in the meninges are most numerous during treatment, and diminish gradually thereafter. Other infiltrative reactions as well as glial proliferation, although pronounced during treatment, become even more intense shortly after the end of treatment. Most reactions increase gradually and reach their maximum between three to six weeks. Only the macrophages in the meninges and the macroglia form exceptions to this, exhibiting the strongest reaction from four to fourteen days after treatment, and then gradually diminish. The diffuseness of the infiltration, so characteristic of cases dying during treatment, becomes gradually less marked towards the end of this period. That is to say, whereas during treatment the infiltration is very intense on all vessels, later the capillary infiltration becomes less, and one finds thicker rings of infiltration on the arterioles and venules.

This increase in the intensity of inflammation is in accord with most previous studies. Kirschbaum [20] reports considerable variation in the intensity of the changes in his twenty-two cases. Nevertheless, the cases showing the severest changes were those dying within the first two weeks, those terminating fatally after one month presented rather slight changes. Only Lehoczky [23] found a diminution of the inflammatory reaction immediately following treatment, but his observations, based on five cases, are hardly convincing in view of contrary findings in 137 cases by various investigators, including forty-seven of my own.

It has been suggested by some, as Sträussler and Koskinas [37], that a change in the character of the histological picture also takes place immediately after malarial treatment, that the "malignant"

paralytic process is at least in part replaced by the "benign" more specific granuloma. As nearly as I can determine this conclusion is based on the finding of miliary gummata in two of their thirty-eight cases. However, since in their original description of these cases [36] they do not mention such findings, it may be assumed that they were not very prominent. Kirschbaum [20] reports finding miliary gummata in two cases out of twenty-two, one of which died shortly after treatment, but he was inclined to view this as merely incidental, and not as indicative of a real qualitative change in the process. Freeman [5], though reporting no miliary gummata, does emphasize the organization of the exudate soon after treatment, in the meninges as well as in the cortical perivascular spaces. The evidence in favour of the view that malaria causes an immediate change to a more specific reaction is slight. That such changes may occasionally be found in general paralysis untreated with malaria was pointed out by Sträussler himself in 1906 [34], and in 1910 [35], and also by Jakob [15]. There is no obvious reason why they may not also occasionally occur in cases treated with malaria, without indicating any causal relationship.

The appearance of gummata in other parts of the body following malarial treatment is very striking. Markuszewicz [25] reported in 1925 a case of typical general paralysis that had had a luetic infection twenty years before. The patient was inoculated with malaria, had nine rises of temperature, and about two months afterwards typical gummata appeared on the forehead and chest. The diagnosis was confirmed histologically. The same year Schulze [30] described three cases that developed typical tertiary syphilitic skin lesions in the first month after treatment. In 1926 Pfeiffer [28] reported a case of general paralysis which had been inoculated with malaria and had twelve elevations of temperature. About six weeks later three hard nodules appeared on both sides with soft centres; they promptly disappeared after injection of salvarsan. In 1927 Kirschbaum [21] described a case of gumma in the throat one and a half years after malarial inoculation; it disappeared in a short time after the use of iodine and salvarsan. The same year Balaban [2] reported a similar case in which gummata developed during malarial treatment.

Interesting as these findings are, they are still too few to permit any definite conclusions. It is conceivable that they may be an indication of the profound influence of the malarial therapy on the entire organism, a disturbance of the usual relationship between the spirochætes and the defence mechanism of the body. There is no conclusive evidence that

the malarial therapy may bring about such reactions in the central nervous system during or soon after treatment.

Several references have also been made to a predominance of lymphocytes. Sträussler and Koskinas, for example, state that lymphocytes characterize the picture, and not plasma cells; Nakamura found a preponderence of lymphocytes, and Freeman [5] says that "even as early as ten days after the onset of fever plasma cells are decidedly scarce" in the meninges. Others deny this, and my own cases do not show any such alteration in the relationship between lymphocytes and plasma cells. It is true that during treatment there was a predominantly lymphocytic infiltration of the meninges, but plasma cells were by no means scarce, and the cortical adventitial spaces showed the usual predominance of plasma cells.

The numerous macrophages found in the meninges during this period should, perhaps, be emphasized; this observation was made also by Sträussler and Koskinas in their first report. Their presence in such numbers would seem to indicate a rather active process, and is in keeping with the general exacerbation of all reactions.

The proliferation of the microglia is one of the most outstanding features of this period. Nakamura [27] found in his cases, two to sixteen days after treatment, an increase of glial nuclei, even the formation of clumps. He does not mention the type of glia, though, from his description, it is likely that he referred chiefly to macroglia. If so, his findings correspond to mine, as in these cases the greatest proliferation of macroglia occurred four to fourteen days after treatment.

In fig. 17 one is at once struck by the strong iron reaction at this stage and its almost precipitous fall in the following period. In this chart only the iron in the blood-vessel walls is indicated, but this may also be considered as representing the iron content of the microglia, since the two were found to run parallel; but the amount in the microglia is far less than that in the walls of the blood-vessels.

Spatz and Metz [31, 32] have pointed out this close relationship between the iron in the blood-vessel and that in the microglia, and are of the opinion that in paralysis the iron is of hæmatogenous origin, and that, as the result of an abnormal permeability of the inner layers of the blood-vessels, iron can easily be taken up from the blood-stream and transported into the tissues. They believe it highly improbable that the iron in general paralysis is the result of katabolic processes in the tissue. These authors also consider iron in the microglia peculiar to general paralysis. The findings in the forty-seven cases studied by me sub-

stantiate these observations. In only two cases did I find a moderately strong iron reaction in the oligodendroglia.

The state of the cerebrospinal fluid has led a number of investigators to the conclusion that an increase in the permeability of the blood-vessels does occur after malaria treatment. I shall return to this question in discussing the changes in the cerebro-spinal fluid.

Period of Restitution.

After three to six weeks there is a steady improvement in the appearance of the cortex, and a gradual recession of infiltration, as well as a diminution of glial proliferation and of iron in the walls of the blood-vessels and microglia. The longer after treatment, the further has this restitution gone. The only exceptions to this are that between six and nine months there may be slight increase of plasma-cells in the meninges, and a slight increase in the proliferation of the macroglia.

In striking contrast to the general signs of improvement is the increase of macrophages in the meninges, the increased intensity of the microglial proliferation and of the iron reaction, found in the cases dying from one to two-and-a-half years after treatment. These reactions do not, however, reach the intensity of the period of exacerbation.

Period of Recrudescence.

It appears that after six months a new flare-up of inflammation may take place in certain cases. Furthermore, this new process differs considerably from the usually accepted picture of general paralysis. Among the four cases examined six to nine months after treatment, such a reaction occurred in one, and among the ten cases examined one to two-and-a-half years after treatment, in five.

Although the intensity of the process differs considerably in each case, the type of the reaction is so similar that the six cases may be considered together.

In each of them some degree of infiltration is found in practically all areas, but the characteristic feature is the small, scattered foci of severe inflammation. In such foci the walls of the blood-vessel are massively infiltrated, in most instances predominantly with lymphocytes, though occasionally there is found, in vessels with marked mesodermal proliferation, a predominance of plasma cells. The infiltrative elements break through the membrana limitans and come to lie free in the nervous tissue around the vessels, and often to such a degree that it is no longer possible to establish the boundaries of the vessel. Numerous blood-

vessels, in addition to the massive infiltration, show a strong mesodermal proliferation and some beginning organization. Here the infiltration tends to lie in layers embedded in this mesenchymal mesh (fig. 12). The lumen becomes narrowed, and may finally be completely obliterated (fig. 10). At times slight paleness is to be seen in the centre of this mesenchymal network, which probably indicates a beginning necrosis. Occasionally, the accumulation of infiltrative elements and mesodermal proliferation become so marked at some place in the vessel as to cause a protuberance on its wall (fig. 13). One sees thus the gradual increase of connective tissue elements from a beginning organization of the infiltration to the formation of a granuloma, with obliteration of the lumen of the blood-vessel and central pallor, and when this process goes still further miliary gummata with necrosis and giant cells develop.

There is a fairly strong iron reaction in the walls of the blood-vessels and in the microglia. Except in the one case examined six months after treatment, the microglia and macroglia are rather slightly proliferated.

Similar findings in cases of general paralysis were described in 1906 and in 1910 by Sträussler. He says [34] "that histologically the two processes develop alongside each other, whereby the luetic foci have served only as a stimulation to the increase in intensity of the paralytic process." In these cases there is no evidence of the paralytic process being exaggerated; on the contrary, the infiltration, except for these foci, is usually less intense.

In 1919, Jakob [15], in a series of fifty cases, described in considerable detail similar inflammatory foci. He dealt especially with cases showing acute exacerbations in association with general convulsive attacks ("Anfallsparalyse"). In such cases, he points out, this type of reaction is most often to be seen. He regarded the paralytic process as a malignant form of brain syphilis to which the defensive mechanism of the body failed to respond, and these inflammatory foci as a vigorous reaction against the invader, a tendency towards a more specific reaction, that is, towards lues cerebri, which is the benign form of cerebral syphilis. Spielmeyer [33], on the contrary, does not believe such inflammatory foci indicate a change in the type of reaction, but includes them in his conception of the histological picture of general paralysis. It is, therefore, merely a question of where the boundary between the two is to be established. Gummata certainly belong to the conception of lues cerebri rather than to general paralysis. As Jakob has pointed out, and as seen in my cases, all transition forms may be found, from the typical general

paralytic perivascular infiltration to gradual increase of mesenchymal tissue with obliteration of the lumen of the vessel, beginning paleness in the centre, later necrosis, and, finally, to the formation of miliary gummata with necrotic centres and giant cells. It seems obvious that these two forms of cerebral syphilis represent differences in the relationship between the defence mechanism of the body and the spirochæte. It is also conceivable that this relationship may, at some time in the course of the disease, be influenced by treatment, or, for that matter, by some general metabolic change. Such an alteration would naturally be expected to modify the histological picture. One would see then, not merely a general paralytic or a cerebral syphilitic process, but an indication of the manner in which the body has responded in defence against the invader.

In the six cases in which I have found evidence of recrudescence, at least it can be said that the process differs from that customarily found in general paralysis; and in its more focal distribution and predominance of mesodermal proliferation, even to the formation of miliary gummata, it tends more towards the type of reaction characteristic of lues cerebri.

It may be recalled that in the other cases, up to two years and a half after treatment, spirochætes were found only once (one case out of twenty-nine). It is well known how rarely spirochætes have been found in the brain after malarial treatment. My own findings are quite in keeping with this, and so one is almost forced to the conclusion that in most of the cases the spirochætes, if not entirely destroyed, are at least greatly reduced in number. It is true that Forster [4] has found them in two cases, in material removed by puncture during life. In the one case the material was removed seven weeks after treatment and so falls in the period of exacerbation; in the same period I found spirochætes in one case out of the first twenty-nine. It may be that at this stage, before the inflammation had subsided, the effects of the malarial therapy have not completed their destruction. In the second case reported by Forster the material was removed six months after treatment and so falls in the period where a recrudescence might be expected.

In striking contrast to the rarity of spirochætes in these twenty-nine cases is the fact that among the six cases which showed a focal distribution of the inflammation spirochætes were found in five. This can hardly be a coincidence. It would appear that this flare-up of focal inflammatory changes is related to the local presence of spirochætes.

When these results are reviewed it seems probable that as a result of the malaria treatment a tremendous destruction of spirochætes takes place, and that if they are not completely destroyed they are, at least, rendered inactive for several months. In some cases where the spirochætes have been incompletely destroyed, they may, after remaining dormant for about six months, regain their virulence, or proliferating, cause a recrudescence of inflammation. Not only is there a new flare-up, but there is a reaction unlike that of general paralysis, suggesting that the malarial therapy has in some way altered the distribution or the virulence of the spirochætes and thus enabled the body to react differently, or that it has altered the reactive ability of the body itself.

In addition to the above more or less uncomplicated cases of general paresis, I have considered a group of six cases which developed, a shorter or longer time before death, convulsive attacks in which they died. These cases ("Anfallsparalyse"), according to some authors (Jakob, Jahnel), present rather characteristic changes, differing considerably from those usually found in general paralysis, and are to be regarded both clinically and histologically as a distinct group.

The following is a short summary of the clinical course and of the histological findings of these cases.

Case 40 (Rei).—(Treated in another hospital, number of rises of temperature unknown.) A maniacal, euphoric and demented patient, developed twelve days after the end of the treatment continuous convulsive attacks which ended in death three days later.

Histological.—With the exception of some endarteritic changes in the small cortical vessels, and small foci of softening in some areas, the usual picture of a moderately severe general paralytic is present.

Case 41 (Mag.).—On admission, March 24, 1921, the patient was confused and expansive, and had marked disturbance of speech.

March 28, 1921: Inoculated with quartan malaria: eight rises of temperature.

May 5, 1921: The patient was little, if any, improved. C.S.F. Wassermann 0-1-3; cells 30; N.A. +.

September, 1921: Blood Wassermann +++; C.S.F. Wassermann 0-0-3; cells 16; N.A. ±; Wb. ++.

January, 1922: He had improved to the extent of being able to help in the ward.

February, 1924: Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells 19; N.A. ++; Wb. +++; mastic: weak paretic curve.

Re-inoculated with quartan malaria, five rises of temperature.

The condition became steadily worse, decubitis developed, he became markedly demented and had seven convulsive attacks, in the last of which he died, November, 1924.

Histological.—This case shows a most marked confusion of the layers of the cortex, and a very severe loss of ganglion cells. Perivascular infiltration, on the other hand, is slight, but is of the type and distribution usually found in general paralysis. Rod-shaped microglia cells are unusually numerous, and the macroglia is strongly proliferated. There is a considerable amount of iron in the walls of the blood-vessels and in the microglia. I was able to find spriochætes in this case, but not in the other five of this group.

Case 42 (Kra.).—On admission, October 30, 1920, the patient was restless, euphoric and expansive. Blood Wassermann negative; C.S.F. Wassermann 3-3-3; cells 119.

November 12, 1920: Inoculated with tertian malaria; sixteen rises of temperature.

January 1921: The patient was much quieter. Blood Wassermann negative; (Stern +++); C.S.F. Wassermann 0-3-3; cells 10; N.A. +. He improved gradually and was discharged March, 1921.

April 29, 1922: Re-admitted: irascible and expansive.

May 2, 1922: *Re-inoculated with tertian malaria*, eight rises of temperature.

July, 1922: He had improved, and was able to work again about the hospital, though was having occasional convulsive attacks. Blood Wassermann negative; C.S.F. Wassermann 3-3-3; cells 42; N.A. ±; Wb. ++.

September, 1922: C.S.F. Wassermann 3-3-3; cells 50; N.A. opalescent: Wb. +; mastic: strong paretic curve.

December, 1922: C.S.F. Wassermann 3-3-3; cells 50; N.A. ±; Wb. ++; mastic: very weak paretic curve.

January, 1923: The patient became gradually demented, and continued having occasional convulsive attacks until he died in status paralyticus, January, 1924.

Histological.—There is a fairly marked confusion of the cortical layers and loss of ganglion cells. The perivascular infiltration is considerable, predominantly plasma cells on the capillaries and smaller vessels, mostly lymphocytic mantles on the larger vessels, which often breaks through into the nervous tissue; an occasional vessel shows strong mesodermal proliferation. The microglia and macroglia are proliferated, though not strikingly so. The iron reaction in the blood-vessel walls and in the microglia is of moderate intensity.

Case 43 (Spr.).—On admission, April 4, 1923, the patient was without insight, excited and irascible. Blood Wassermann +++.

April 30, 1923: Inoculated with tertian malaria, eight rises of temperature. During treatment, blood Wassermann ±; C.S.F. Wassermann 3-3-3; cells 48; N.A. ±; Wb. +.

June 1, 1923: Blood Wassermann negative (Stern ++); C.F.S. Wassermann 1-2-3; cells 5; N.A. +; Wb. ++; mastic: very strong paretic curve.

July, 1923: Blood Wassermann negative; C.S.F. Wassermann 1-2-3; cells 18; N.A. slightly opalescent: Wb. opalescent.

August, 1923: Blood Wassermann negative; C.S.F. Wassermann 0-0-0; cells 31; N.A. slightly opalescent; mastic: very strong paretic curve.

September, 1923: Blood Wassermann negative; C.S.F. Wassermann 0-0-2; cells 19; N.A. slightly opalescent; mastic: typical lues cerebri curve.

October, 1923: Blood Wassermann negative: C.S.F. Wassermann 0-0-0; cells 43; N.A. slightly opalescent; mastic: lues cerebri curve.

November, 1923: Blood Wassermann negative: C.S.F. Wassermann 0-0-0; cells 6; N.A. slightly opalescent; mastic: weak paretic curve.

December, 1923: The patient had improved enough to be discharged, though he still exhibited considerable defect.

November, 1924: Readmitted because of excitability, profanity and theft. Blood Wassermann negative; C.S.F. Wassermann 0-1-2; cells 120; N.A. slightly opalescent; mastic: very strong paretic curve.

April 29, 1925: After progressive deterioration the patient began to have convulsive attacks which continued at frequent intervals until his death on May 1, 1925.

Histological.—This case presents the usual paralytic changes of very severe degree, marked architectural disturbance and loss of nerve cells, strongly infiltrated vessels, numerous cells breaking through into the nervous tissue, strongly proliferated microglia and rather intense iron reaction in the microglia and walls of the blood-vessels.

Case 44 (Tho.).—On admission, May 22, 1922, the patient was confused and excited. Blood Wassermann negative (Stern +++); C.S.F. Wassermann 1-3-3; cells 67; N.A. +; Wb. ++; mastic: strong paretic curve.

June 2, 1922: Inoculated with tertian malaria, seven rises of temperature.

July 2, 1922: Blood Wassermann +; (Stern +++); C.S.F. Wassermann 0-0-2; cells 36; N.A. +; Wb. ++.

August, 1922: C.S.F. Wassermann 1-3-3: cells 30; N.A. ±; Wb. +.

September, 1922: Blood Wassermann negative; C.S.F. Wassermann 0-1-1; cells, 22; N.A. ±; Wb. ++.

October, 1922: Blood Wassermann negative; C.S.F. Wassermann 0-0-1; cells 42; N.A. ±; Wb. ++. The patient was discharged in a good remission.

December, 1923: Readmitted confused and excited.

April, 1924: The patient had become considerably demented and wholly indifferent, and was having light convulsive attacks which continued until death in status paralyticus, September, 1924.

Histological.—The parenchymatous changes (architectural disturbance and loss of nerve cells) is only of moderate severity. The infiltration, too, is slight, except for a thick lymphocytic ring around an occasional larger cortical vessel. The iron content of the blood-vessels and of the microglia is small, but the microglia is strongly proliferated.

Case 45 (Bec. J.).—On admission, August 4, 1920, he was confused, and evidenced considerable mental impairment. Blood Wassermann +++ C.S.F. Wassermann 3-3-3, cells 32; N.A. ++.

August 20, 1920: Inoculated with tertian malaria; fourteen rises of temperature.

October, 1920: He had improved slightly, was helping about the ward, though quite without insight into his illness.

February, 1921: Condition essentially the same. Blood Wassermann + + ; C.S.F. Wassermann 1-3-3; cells 13; N.A. + + ; Wb. + +.

June, 1922: The patient was indifferent, euphoric, and had occasional convulsive attacks. He continued slowly downhill and having attacks, in one of which he died, July, 1925.

Histological.—Infiltration is very slight, both in meninges and in the perivascular spaces of the cortex. The glia is little proliferated. The quantity of iron in the walls of the blood-vessel and macroglia is small. The arrangement of the ganglion cells and of the cortical layers is rather well preserved, but there is considerable loss of cells. In all areas the ganglion cells show severe "acute swelling."

As previously mentioned, in such cases as these ("Anfallsparalyse") one expects to find changes of a rather unusual sort, deviating considerably from the common picture of general paralysis and occupying a special position as regards the frequency with which spirochætes may be found.

In the first place spirochætes were found in only one of the six cases. Every case died during an epileptic attack and according to Jahnel [13] these are just the cases in which spirochætes should be present in great numbers. He says that: "During the chronic course of the disease there occasionally appear acute exacerbations, which we designate as paralytic attacks. It is not seldom that death takes place in a paralytic attack. Anatomically, corresponding to this 'attack' there is a sudden and massive destruction ('Untergang') of nervous tissue; parasitologically, a strong and widespread proliferation of spirochætes in the brain. The death in a paralytic attack is not only a 'brain death' but also a 'spirochætal death'; we have before us one of those cases in which the agent of syphilis is the direct cause of death." Jakob [15] agrees with Jahnel, in that the attack corresponds to a strong and widespread proliferation of spirochætes, and Hermel [9] was able to find them in 80 per cent. of such acute ("Anfallsparalyse") cases. Others, as Marinesco and Minea [26], Levaditi, Marie and Bankowski [24], have also emphasized the richness of spirochætes in cases dying soon after or in attacks. In explaining the failure to find spirochætes in such cases, he says (p. 35): "It seems quite intelligible that in such cases spirochætes may not be found, especially when the interval between the attack and death is more than a few days (two to

three)," that is to say, that during such an interval the antibodies called forth by this very massive proliferation of spirochætes may be able to destroy the agent of the attacks.

All of these patients showed the acute exacerbations, such as, according to Jahnel's explanation, correspond to a massive proliferation of spirochætes and, as they died in the attacks, there was no interval during which the activity of the antibodies might destroy the spirochætes and thus account for the failure to find them. One case of course died three weeks after treatment, which may or may not be held responsible for the inability to find spirochætes. On the other hand, the last five cases died at intervals of eight months to five years after treatment, and it is hardly conceivable that any influence of the treatment on the spirochætes could be manifested after such a long time, and, as will be pointed out, in these cases the spirochætes apparently may begin to proliferate again after six months.

These cases would then seem to lend more support to the theory of Ehrlich [3], that these acute exacerbations are due to a rapid absorption of endotoxins liberated by a sudden massive destruction of spirochætes by antibodies ("thus the apparent paradoxical findings, death without spirochætes"), and to the views of Hauptman [7], who also regards the paralytic attacks as clinical manifestations of destruction of the spirochætes by the antibodies, the resulting toxin producing a clinical picture comparable to an anaphylactic shock. Nor are these latter theories necessarily refuted by the frequency with which spirochætes have been found in such cases by many authors. It is conceivable that the finding, or the failure to find, spirochætes might depend upon whether or not, at the time of examination or death, the antibodies had succeeded to a certain degree in the destruction of the spirochætes. In either case one might expect convulsive attacks, until the spirochætes become so reduced in number or virulence as to constitute no longer a stimulus to the formation of antibodies, or else that the body loses its power of reacting to this stimulus. Jahnel, although denying an important rôle to the endotoxins in producing these severe clinical manifestations, does attribute the failure to find spirochætes in such cases to their destruction by antibodies, although he is of the opinion that the attacks tend to appear before the antibodies become of importance.

The next point is the degree of mesenchymal proliferation present in these cases. Jakob [15] stresses the frequency of miliary gummata, or gummatous changes in the blood-vessels, in the usual cases of general

paralysis, especially in those with many acute exacerbations leading rather rapidly to death, the so-called "Anfallsparalyse." Among fifty such cases he found gummatous changes of the blood-vessels in twenty-two. He also emphasizes the frequency of severe endarteritic changes. In only one of these six cases, however, did some of the vessels present marked mesenchymal proliferation, which may possibly represent the early stage of a developing gumma. In only one case were marked endarteritic changes of the small cortical vessels found. These six cases can, of course, offer no refutation to the assertion of Jakob, that the reaction of the mesodermal tissue in such cases is unusually strong, since his conclusions are based on the study of fifty cases. It is conceivable, accepting his conclusions to be correct, that the failure of such a reaction in these cases may be related to the malarial treatment. They all, with the exception of one case, show very severe changes, and contrast sharply with the other cases (according to interval after treatment), and so seem to justify their being regarded as a distinct group.

In considering the alterations in the histological picture that may follow malaria, and possibly may in part be due to some change in the relationship between the parasite and the reactive ability of the body brought about by this treatment, two other cases may be briefly described, which show a reaction quite different from those previously considered. These are two cases with syphilitic endarteritis of the small cortical vessels and their clinical courses are as follows:—

Case 46 (Bod.).—Admitted April 2, 1922. His symptoms dated back four years. Commencing with headaches and irascibility, he later began drinking heavily, and was at times confused and expressed expansive ideas. His pupils were unequal and reacted sluggishly to light, the left side of his face was weak, and his tongue deviated to the left. Blood Wassermann +; C.S.F. Wassermann 3-3-3; cells 132; N.A. +.

In May, 1922, he was inoculated with tertian malaria, and had three rises of temperature.

October, 1922: He had improved sufficiently to be discharged.

December, 1922: In another hospital, he was twice inoculated with malaria, having one and five rises of temperature respectively. Following this there was some clinical improvement. March, 1923: Blood Wassermann + + + +; C.S.F. Wassermann 3-3-3.

Towards the end of 1924 he commenced expressing paranoid ideas, was resistive and refused nourishment. Later he developed pneumonia, and died March 14, 1925.

Case 47 (Rie.).—Admitted April 13, 1921. For one year he had shown emotional instability, poor memory, irascibility and some confusion. On

admission he was indifferent, wholly without insight, at times profane and had considerable disturbance of speech. Pupils were unequal and reacted sluggishly to light. There was right-sided facial weakness. Blood Wassermann +++; C.S.F. Wassermann 3-3-3; cells 37; N.A. ++; Wb. +++.

July, 1921: Inoculated with tertian malaria, six rises of temperature.

No improvement followed. He continued indifferent and manifested increasing dementia, becoming finally apathetic. April, 1925: Blood Wassermann +++; (Stern, ++++); C.S.F. Wassermann 0-1-2; cells 8; N.A. slightly opalescent; Wb. opalescent; mastic: typical lues cerebri curve. He died September 9, 1926.

Histologically the two cases are very similar. The meninges show considerable connective tissue thickening, but little infiltration. The cortical architecture is fairly well preserved in spite of a rather marked falling out of ganglion cells. The cortical perivascular infiltration is that of general paralysis, but is of a very mild degree. Most striking are the changes in the small vessels themselves. There is a fibrous tissue thickening, with marked increase of nuclei, and on cross section one sees a thick wall and a very narrow lumen. The vessels coursing down from the meninges appear as streaks of connective tissue, rich in nuclei, and often very tortuous. The nuclei in these cases for the most part are small, deeply stained and often pycnotic. This probably indicates that these changes are not of very recent date, at least in many cases of syphilitic endarteritis [Jacob (16)] the endothelial and adventitial cells appear more progressive than regressive. There is considerable proliferation of macroglia, rich in protoplasm and often bunched together in tufts. On the other hand the microglia is little proliferated and the typical rod-shaped cells are almost entirely absent. The iron content of the walls of the blood-vessels and of the microglia is very slight.

In reviewing these cases there is obviously no parallelism between the clinical course and the pathological findings in the brain. Even the cases with slight changes did not differ clinically from those with very severe changes. That such inconsistencies occur in general paralysis is well known. In 1904, Alzheimer [1], in his classical work on general paralysis, described the severest paretic changes in a case committing suicide before any symptoms appeared. Similar observations have since been recorded. It is generally accepted that there is no real parallel between the intensity of inflammation and the severity of parenchymatous changes.

This is not surprising if the parenchymatous changes be regarded as degenerative incident to the presence of spirochætes in the body, whether a direct injury by the spirochætes themselves or by some indirect toxic influence, and the inflammation as indicating the reaction of the body to the invader. In the cases with slight changes it would seem that

the subsiding inflammation is due to the fact that the invader has been destroyed, or at least so reduced in numbers (in only one case in twenty-nine were spirochætes found) as no longer to constitute a stimulus to the defensive mechanism of the body. The spirochætes, however, have so altered the metabolism of the nerve-cells, or in their reduced numbers continue to give rise to toxins to the extent of obviating functional recovery, despite the fact that considerable restitution has taken place in the arrangement of the cortical layers and nerve-cells.

In comparing the pathological findings with the serological reactions, there also appear some inconsistencies. The relationship among the ten cases studied pathologically one to two-and-a-half years after treatment, is very striking. In the five cases in which the histological changes were slight there was improvement serologically, whereas the five cases with severe changes had in general no alteration of the reactions, or else it became worse. In contrast with this, of the three cases examined three to five years after treatment, in one with severe changes there was some improvement, and in another with less severe changes the serology was very slightly worse after treatment. Among the six cases characterized by epileptic attacks, there is no apparent relationship between severity of histological changes and the degree of alteration of the reactions. Is it merely a coincidence that the serological alterations in the ten cases studied one to two-and-a-half years after treatment tend to run parallel with the severity of the inflammatory reaction, or is it possible that a stationary condition, or an increased intensity of the serological reactions, may be taken as an indication of a still active inflammatory process? Were the latter the case, then very interesting relationships become obvious. An improvement in the serological reactions would indicate a standstill or regression of inflammation, following the destruction of the spirochætes. (I refer to the almost negligible spirochætal findings in such cases—one case in twenty-nine.) That clinical improvement does not coincide in some cases may mean that, although the spirochæte has been eliminated, the disturbance to cell metabolism has been so severe that functional recovery is no longer possible. In such cases renewed therapeutic efforts would be of no avail. On the other hand, if there has been no improvement in the serological reactions up to six months or longer, it would indicate the presence of spirochætes which, as my cases seem to indicate, may after six months cause a new flare-up of inflammation. Such cases might be benefited by renewal of treatment. It is, of course, impossible to

formulate any definite conclusions from such limited observations, but they suggest at least a possible correlation between the histological process and the serological reactions.

One of the most striking serological reactions is the mastic. Kirschbaum and Kaltenbach [19, 22] have attached a prognostic value to it. They noted that it often changes to a lues cerebri type of curve on improvement, and when the patient becomes worse it shifts back towards the general paralytic type. Among the cases I examined the mastic reaction was studied in only sixteen, and, unfortunately, in these cases not frequently enough to permit very definite conclusions. Nevertheless, certain relationships stand out which seem deserving of mention. In only one case among those showing histological improvement was the mastic reaction studied after six months. In this case the reaction became weaker, and approximated the lues cerebri type. Averaging the curves of all the cases for each period after treatment, it was possible to construct a curve (fig. 17). It is at least interesting that this curve runs almost parallel with the severity of the histological changes. Between four to fourteen days it takes up a position even more typical for general paralysis than before treatment. Between three to six weeks it shows a precipitant drop, and, except for a slight secondary rise, remains at this low level until the period six to nine months is reached. After six months it shows a very marked ascension, reaching a level slightly more typical for general paralysis than before treatment. Thus it is seen that this tremendous secondary rise corresponds to the period where a new flare-up of inflammation may take place.

Another serological reaction to which considerable importance has been attached is the hæmolysin reaction of Weil and Kafka [38,39]. These authors consider that it indicates an increased permeability of the meningeal blood-vessels, and found it positive in most cases of general paralysis. Pötzl [29] found it disappearing after malarial treatment, generally after about two months. Horn's [11,12] investigations were essentially in confirmation. Hauptmann [8] sees in these observations evidence in support of his hypothesis that the nervous tissue is injured by substances escaping from the blood through the meningeal blood-vessels, which are rendered more permeable as a result of injury by toxins incident to the presence of spirochætes in the body.

Spatz and Metz (31,32) have made an extensive study of the iron reaction in the brain and have called attention to the diagnostic value of its presence in the microglia in general paralysis. They also found considerable iron in the walls of the blood-vessels, and a striking

parallelism between this and the iron content of the microglia. They concluded that the iron in the microglia was of hæmatogenous origin and thus that in general paralysis the blood-vessels are more permeable. My findings are in keeping with these. Directly after malarial treatment there is a great increase of iron in the blood-vessels and microglia; after three to six weeks, with the improvement in the histological picture, the iron content rapidly diminishes. These observations seem to indicate an increased permeability of the blood-vessels during and directly after treatment, and then a rapid approach towards normal.

Hoff and Silberstein [10] have found an increase of the opsonic index for streptococci, staphylococci and colon bacilli in the blood and spinal fluid of patients during malarial treatment, and although their results with spirochætes were not satisfactory, nevertheless there was some evidence that they may be taken up by phagocytic cells. Furthermore, the spirochætes treated with spinal fluid and leucocytes of these patients soon disintegrated and produced no testicular lesions in rabbits, whereas when spinal fluid and leukocytes of untreated patients were employed the spirochætes retained their motility and produced typical syphilitic lesions.

I may recall here the presence of many macrophages in the meninges soon after the end of the fever. This may be an histological expression of increased phagocytic power. Sträussler and Koskinas [36] also noted numerous macrophages in the meninges directly after treatment.

Summary and Conclusions.

(1) In sixteen cases coming to post-mortem within six weeks after malarial treatment, the histological changes may be described as a severe diffuse general paralytic process. Outstanding is the strong glial proliferation and the richness of iron in the walls of the blood-vessels and microglia. The increase of iron probably indicates an increased permeability of the blood-vessels. The presence of numerous macrophages in the meninges may be the expression of an increased phagocytic power, evidence of which has been found in studies on the cerebrospinal fluid by others. Spirochætes were found in one case.

No evidence was found indicating a change to a more specific type of reaction. In the earliest stages only was a considerable predominance of lymphocytes in the meninges present, whereas in the cortical perivascular spaces plasma cells predominated throughout.

Towards the end of this period the infiltration tends to increase on the arterioles and venules and decrease on the capillaries.

(2) Following this period of exacerbation of inflammation there is a period of restitution. In thirteen cases, after six weeks and up to two-and-a-half years, there is a gradual improvement in the arrangement of the cortical layers and nerve-cells, and at the same time a rather rapid and considerable reduction of infiltration and of glial proliferation.

The very considerable reduction of iron in blood-vessels and microglia adds support to the serological evidence of a decrease in the permeability of the blood-vessels.

During the interval one to two-and-a-half years there is a secondary increase of macrophages in the meninges, of microglia, and of iron in the walls of the blood-vessels and in the microglia. In none of these cases were spirochætes found. The fact that in the twenty-nine cases thus far considered spirochætes were found only once, suggests strongly that the malarial treatment has brought about a tremendous destruction of them.

(3) Among the cases coming to autopsy from six months to two-and-a-half years after treatment, six are characterized by scattered foci of intense inflammation in which the mesodermal tissue is strongly proliferated, even to the formation of typical miliary gummata in one. Spirochætes were found in five of these six cases. It seems probable that these are cases in which the invader was not successfully exterminated, and after six months is again able to regain its virulence and to proliferate.

In considering the serological reactions of these cases it is found that no improvement followed treatment, whereas in the cases with histological improvement there was also serological improvement. This suggests the possibility of recognizing the cases in which extermination of the spirochætes has not been successful, and therefore the liability of a secondary flare-up of the process. Such cases might benefit by a new therapeutic effort.

(4) Three cases, three to five years after treatment, follow less clearly the above rules. This may be taken to mean that any influence of the malarial treatment has been lost after three years.

(5) Six cases are described that were characterized by frequent convulsive attacks, and which died in such attacks. The above findings cannot be correlated with these cases. It seems likely that they may represent a special group.

(6) Two cases of syphilitic endarteritis of the small cortical vessels were found among the forty-seven examined, suggesting that as a result of the malarial treatment the general paralytic process may, in an occasional case, be replaced by such a reaction.

(7) In one case which terminated during a remission the histological picture was that of " stationary paralysis."

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INCREASED INTRACRANIAL PRESSURE.

BY JOHN S. B. STOPFORD, M.D., F.R.S.

Professor of Anatomy in the University of Manchester.

Introduction.

In recent years a considerable advance has been made in our knowledge of the factors influencing intracranial tension, but there still remain many problems connected therewith which require elucidation. Until more complete information is available with regard to the factors which determine the normal intracranial pressure, it remains difficult to ascertain precisely the mode of causation of such an abnormal condition as increased intracranial tension. Nevertheless, careful investigations of pathological states must stimulate research upon the outstanding anatomical and physiological difficulties, and may even throw considerable light upon these problems.

Reference to the anatomical position and circulation of cerebro-spinal fluid within the cranium shows that its pressure must be the same as intracranial pressure, and therefore it is possible to express intracranial tension in terms of cerebro-spinal fluid pressure. The cranium being practically a closed box, any alteration of intracranial tension must be due to a change in one or more of the three elements—brain, blood and cerebro-spinal fluid—which it contains. The experimental work of Weed and his co-workers has shown that variation in one content may, within certain limits, be compensated for by modification in the volume of one or both of the others. Dixon and Halliburton [3] corrected the opinion expressed by Leonard Hill [5] that the cerebro-spinal fluid and cerebral venous pressures were the same. These observers showed that the cerebro-spinal fluid pressure was influenced passively, to a slight extent, by alteration of the arterial and venous pressure, but that this influence was trivial compared with the much greater changes which resulted from an increased production of the fluid. Dixon and Halliburton further demonstrated that an alteration of the cranial venous pressure produced a similar, but not identical, alteration in the cerebro-spinal fluid pressure, and conversely an increase

in the latter pressure caused passively a slighter rise in the cranial venous pressure. Weed and Hughson [15] have confirmed these results and proved in a large series of experiments that in almost every case the cerebro-spinal fluid pressure was considerably higher than that of the pressure in the hinder part of the superior longitudinal sinus. Although it seems now definitely established that the cerebro-spinal fluid pressure is higher than the venous pressure in the sinuses, which have strong walls and can therefore withstand considerable pressure, it is not legitimate to assume, as Brain [1] has pointed out, that the pressure in the small cerebral veins is as low as that in the large intracranial sinuses. It appears highly improbable that the pressure in the thin-walled and poorly supported cerebral veins is less than the fluid pressure, because if this is the case it is difficult to understand how the cerebral veins can remain patent and avoid being compressed by the higher pressure around them. Most of the superior cerebral veins pass obliquely forward to pour their contents into the superior longitudinal sinus against the flow in the sinus. This will have the effect of raising the pressure in the veins above that in the sinus, and the arrangement, which otherwise seems a very curious one, may well be for this purpose, and illustrates once again the inter-relationship of function and structure.

The intracranial arterial pressure is also under normal circumstances a factor in the maintenance of cerebro-spinal fluid pressure, but it has been shown that a sudden and considerable alteration in the arterial pressure is required in order to influence appreciably the pressure of the fluid. While it is clear that the cerebro-spinal fluid pressure is dependent upon the intracranial arterial and venous pressures, and may be modified by changes in one or the other, it appears to be more independent of both than many of the earlier observers realized. Weed [14] has stated that "the pressure of the cerebro-spinal fluid may be considered to be relatively independent of both, in that normally it maintains an individual fairly constant level below that of the intracranial arteries and somewhat above that of the intracranial veins." For reasons emphasized by Brain and already mentioned, it would be more accurate to substitute large intracranial sinuses for intracranial veins, in the above statement. There is evidence [15, 16, and 17] that the fluid pressure may be altered independently of any change in the intracranial and systemic vascular pressures. Furthermore, from observations in the experimental production of internal hydocephalus and from other studies, it is evident that the cerebro-spinal fluid may still be produced when the intraventricular pressure

has been considerably raised above the normal. We do not as yet know whether the cerebro-spinal fluid is a secretion or of the nature of a dialysate, but evidence seems to be accumulating in favour of the latter. Provided the composition of the plasma remains constant, it has been shown that the rate of production varies directly with the capillary pressure, and that this is dependent more upon venous than upon arterial blood-pressure.

Raised Intracranial Tension.

The establishment of the greater independence of the cerebro-spinal fluid pressure has been stressed because it seems to be of importance when we refer to such an abnormal condition as the increased intracranial tension which is so frequently associated with a tumour within the cranium.

It is difficult to believe that the introduction of an additional mass within the closed box can *per se* be the cause of the raised tension, since a large frontal tumour may fail to produce it, whereas a small one in the subtentorial region may cause profound manifestations of increased intracranial pressure. It is not easy to understand why the three normal contents of the cranium should be able to compensate for the introduction of an additional mass in certain sites and not in others, but it would appear that in certain positions the tumour is able to affect one or more of the contents in such a way as to upset the conditions upon which normal tension depends. Unfortunately, we do not yet know precisely the factors which determine the normal cerebro-spinal fluid pressure, which Weed has estimated as equal to 110 to 130 mm. of Ringer's solution. Weed [15] thinks the normal pressure "may be largely determined by the balance between the constant new production within the cerebral ventricles and the absorption into the dural sinuses: this pressure of the cerebro-spinal fluid becomes dependent also upon intracranial, arterial and venous pressures, not only because of the relation of these latter pressures to the production and absorption of the fluid, but because of the constancy of volume of the intracranial contents."

From these introductory references it will be appreciated that it is unlikely that any change in the pressure in the intracranial sinuses or arteries could cause the great elevations of intracranial pressure which are not unfrequently associated with cerebral tumour. The profound and early evidence of raised intracranial tension occurring with subtentorial growths might suggest the possible compression of the lateral

sinuses as they leave the cranial cavity through the jugular foramen. It might be thought that such obstruction would induce a pressure in the superior longitudinal sinus greater than the cerebro-spinal fluid pressure, and so delay the absorption of the fluid and lead to its accumulation within the cranium, with consequent increase of tension. It is quite clear, however, on anatomical grounds, that such a rise of pressure in the sinuses could only be of very short duration on account of the presence of numerous emissary veins which would provide a collateral drainage and rapidly reduce the venous pressure.

On reviewing the three contents of the cranium and their relation to one another, it appears most probable that the tumour raises intracranial tension through the cerebro-spinal fluid. There are also indications that in cases of increased intracranial pressure the cerebro-spinal fluid is commonly present in larger quantities than in the normal cranium. The excess may be in the subarachnoid space, in the ventricles, or in both these positions, and its situation will be more fully discussed later. Such an increase in the amount of fluid beyond a point at which it might be compensated for by the other cranial contents would obviously raise intracranial tension, and could be created either by excessive production, interference with absorption, or obstruction somewhere between the sites of its production and absorption.

Before discussing these three possible disturbances of the balance which normally exists between the production and absorption of cerebro-spinal fluid, it is more convenient to refer to the factors which appear to influence the occurrence or absence of raised intracranial pressure in cases of tumour. From an analysis of large numbers of patients suffering from intracranial tumour, it is generally agreed that the anatomical site of the growth is of first importance with regard to the occurrence of increased tension. The rate of growth and size of the tumour also seem to play some part, but they appear to be of distinctly less significance than the anatomical situation. The presence or absence of œdema of the nervous tissue round the tumour needs consideration, but it cannot be of such primary importance as the site of the neoplasm, as there is no reason why œdema should occur earlier and more constantly in one position than in another. When œdema does supervene, it must add to the mass within the cranium and thus, like the size of the tumour, consitute a factor which must bear on the problem. However, as œdema may develop round a tumour in any position, it cannot be regarded as of the same significance and importance as the site of the growth.

The histological character of the growth bears no relation to the occurrence or absence of increased intracranial pressure. Since the site of the tumour is the factor of primary importance, it is likely that the causation of the raised pressure must be of mechanical origin. The influence of the rate of growth, size of the tumour and possibly the occurrence of œdema, is also compatible with a mechanical origin, since a slow-growing or small growth would often permit some compensation for the mechanical disturbance to take place, which is less possible for growths rapidly increasing in size, or surrounded by a considerable amount of œdematous tissue. When reference is made to the situation of tumours which are most frequently associated with manifestations of a raised intracranial pressure, further light is shed on the problem. It is well known that mid-brain and subtentorial tumours constantly and at an early stage cause a raised intracranial tension, whereas tumours of the pons do not as a rule, unless they invade neighbouring parts, and particularly the subtentorial region. Furthermore, on studying records of patients, it is discovered that signs of increased tension are often absent in the case of growths of the frontal region, and less frequently absent in the parietal lobe, and rarely absent in the occipital region.

With the object of determining the importance of site, I recently abstracted the post-mortem records of all cases of primary intracranial tumour (excluding meningeal growths) at the Manchester Royal Infirmary, for the twenty-five years from 1901 to 1925 inclusive. In all there were eighty-one reports, but of these cases I could only procure clinical notes in fifty-nine, and these alone can be used to determine the influence of site upon the occurrence of symptoms of intracranial pressure. The accompanying table of these cases demonstrates very clearly the influence of site, and supports the general conclusions to which I have just referred. A further analysis of these cases will be made later.

Position of growth	Number of cases	Pressure symptoms	
		Present	Absent
Frontal	9	6	3
Fronto-parietal	6	4	2
Parietal	8	6	2
Temporo-sphenoidal and temporo-occipital	5	4	1
Parieto-occipital	9	8	1
Occipital	5	4	1 *
Cerebellum	6	5	1
Medulla	4	2	2
Pons	5	3	2
Cerebello-pontine angle	2	2	0
Total	59	44	15

* Died at an early stage from haemorrhage in the opposite cerebral hemisphere.

Returning to the question as to whether tumours in certain situations can interfere with the absorption of the cerebro-spinal fluid, obstruct its flow or cause an increase in its production, the first of these possibilities may now be considered. Recent research [12 and 13] has provided considerable knowledge regarding the absorption of cerebro-spinal fluid through the arachnoid villi into the venous sinuses. In view of this information it is difficult to see how a tumour could affect the drainage of the fluid, and impossible to understand how a growth in the mid-brain or subtentorial region could interfere with absorption more than a growth in the pons or frontal region. As stated previously, any compression of the venous sinuses, as in the neighbourhood of the jugular foramina, would be soon compensated for by the numerous emissary veins. Consequently it seems justifiable to exclude with confidence the possibility of interference with absorption of cerebro-spinal fluid as being the primary cause of the raised intracranial pressure. For reasons which will be alluded to subsequently, it is possible that in the later stages of some cases with great dilatation of the ventricles absorption may be interfered with, but it is a secondary factor in the ætiology of raised pressure.

Both the other possible causes need much fuller consideration. It does seem practicable for tumours occupying the sites which are known to be most often associated with raised intracranial tension, to cause compression of the great vein of Galen, which receives blood from the choroid plexuses of both lateral and the third ventricles. Such obstruction to the venous drainage must produce an increased capillary pressure in the choroid plexuses, which in turn will lead to an increased production of cerebro-spinal fluid. Dandy [2] has submitted experimental evidence of the latter statement, since he has demonstrated that occlusion of the great vein of Galen in dogs, provided it occurs at the origin of the vein, and that the development of a collateral circulation is thus prevented, causes internal hydrocephalus on account of the over-production of fluid. In addition to this experimental evidence, a few cases have been reported of internal hydrocephalus caused by thrombosis of the great vein of Galen, or obstruction of the straight sinus by external pressure or thrombosis. Since venous obstruction has long been regarded as a factor in the causation of some cases of hydrocephalus, it is necessary to notice that Dandy states that in none of his thirty patients suffering from this condition was there any obstruction of the vein. I mention this probably very rare cause of hydrocephalus merely in support of the experimental evidence that

obstruction to the venous drainage from the choroid plexuses can induce an excessive production of cerebro-spinal fluid: consequently it seems necessary to consider further whether the raised intracranial pressure associated with brain tumour is caused by excessive production of cerebro-spinal fluid due to venous obstruction, and this will be discussed in detail when a fuller reference has been made to the position and relations of the great vein of Galen.

Before this is done it is necessary to mention the third possible cause of the raised pressure, viz., obstruction at some point to the normal flow of cerebro-spinal fluid. It is well known that tumours in certain situations, particularly those in the posterior fossa of the skull, may induce distortion and displacement of the brain-stem. This has been thought by many to lead to obstruction of the flow of cerebro-spinal fluid through the narrow aqueduct of Sylvius, which will readily cause dilatation of the lateral and third ventricles, and so explain the ætiology of increased intracranial pressure. Since subtentorial growths are most constantly manifested by signs of increased pressure at an early date and are most likely to bring about distortion and displacement of the brain-stem, this possibility must also be considered in connection with its clinical and pathological findings.

Great Vein of Galen.

The two veins of Galen which pass backwards in the velum interpositum are each formed by the vein from the choroid plexus of the lateral ventricle and the vein of the corpus striatum. The latter receives small tributaries from the wall of the anterior horn of the ventricle and the septum lucidum; whilst lying in the velum interpositum the veins of Galen receive blood from the choroid plexuses of the third ventricle and are joined by several small veins from such structures as the corpus callosum, quadrigeminal bodies, and optic thalami, and may receive one large venous channel named the basilar vein. The basilar vein is formed by the anterior cerebral vein, the deep Sylvian vein, and the inferior striate veins which emerge through the anterior perforated spot. After curving round the midbrain, where it receives numerous small branches, the basilar vein either joins the vein of Galen of its own side, the great vein of Galen, or the straight sinus. When it is a tributary of the vein of Galen, the junction occurs exactly at the point where the two veins unite to form the great vein of Galen. The great vein of Galen, as explained in an earlier paper [11] does not take a direct course to the straight sinus, but curves

round, and is throughout in intimate contact with the splenium of the corpus callosum. Thus, from its origin, the vein passes at first backwards and upwards, and then forwards and upwards, to reach the hinder end of the inferior longitudinal sinus (fig. 1). The relation with the splenium is always most intimate, and the vein opens into the sinus like the tributaries of the superior longitudinal sinus—e.g., against the flow of the current in the sinus. Taking this course, which is much more vertical than horizontal, it will be at once noticed that anything which raises the tentorium is certain to exert tension upon the vein and

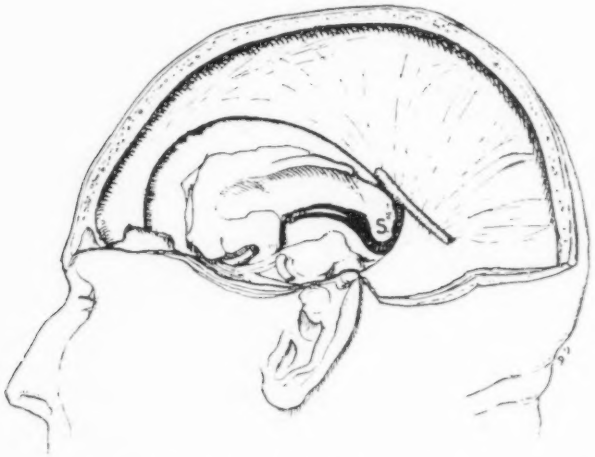

FIG. 1. Drawing of dissection to show the relation of the great vein of Galen to the splenium. Part of the inferior longitudinal and straight sinuses have been incised to display the termination of the vein. S. = splenium.

cause it to be compressed against the splenium. It is important to remember that the tentorium may be elevated directly, as by pressure from below, or indirectly, as from lateral deflection of the falx cerebri, owing to the mode of attachment of this structure to the tentorium. The course and relations of the great vein of Galen are not represented in many of the modern anatomical textbooks, but are figured, as I have described, in several of the older volumes. They are well shown in many of the plates published in the classical memoir by Key and Retzius [9] and can be demonstrated in a dissection made from the side, without disturbance of the falx cerebri or tentorium. Cutting of these partitions, as customary in the usual method of removal of the brain, destroys the correct relations and general course of the vein.

The great vein of Galen, in addition to the basilar vein which may empty into it, receives some of the superior cerebellar veins, and also veins from the hinder and medial surface of the cerebrum. Compression of the great vein of Galen would undoubtedly obstruct the flow into it from these cerebellar and cerebral veins, but efficient compensation would be possible through venous communications, which are known to be free in the case of both superficial cerebral and cerebellar veins. These communications would probably prevent any permanent passive congestion of the cerebrum or cerebellum, but would obviously not relieve the engorgement of the tributaries from such structures as the choroid plexuses, as the obstruction is in front of the junction of these cerebral and cerebellar veins with the great vein of Galen. When the basilar vein joins the great vein of Galen or the straight sinus, compression of the great vein of Galen against the splenium would clearly prevent the basilar vein from relieving passive engorgement of the radicals of the veins of Galen, including the veins from the choroid plexuses of the third and lateral ventricles. When the basilar vein opens into the veins of Galen, the junction is always found just at the point where these two fuse to form the great vein of Galen, and their orifices are in such a position that partial occlusion at least would appear inevitable when the great vein was pressed upwards against the splenium; in fact, it is likely that with elevation of the tentorium the vein would initially be compressed at this point. Therefore, wherever the basilar vein terminates, it seems quite impossible for it to compensate satisfactorily, as regards the venous drainage from the choroid plexuses, for obstruction to the flow in the great vein of Galen. Thus, on anatomical grounds, compression of the great vein of Galen by elevation of the tentorium, either directly by pressure from below, or indirectly by deflection of the falx cerebri, does seem a reasonable possibility. Such an obstruction will impede the venous return from the choroid plexuses and cause an increased capillary pressure in them. This condition would induce an excessive production of cerebro-spinal fluid, since investigations have proved that the rate of formation of the fluid varies with the capillary pressure in the choroid plexuses. There is no doubt that deflection of the falx can and does occur commonly in association with supratentorial growths and particularly with those in the more posterior part of the cerebral hemisphere, and there is no doubt that such deflection will elevate the tentorium. There may, however, be some hesitation in accepting the suggestion that subtentorial growths can raise by pressure from below such a strong structure

as the tentorium. Investigations of the shape of the ventricles in cases of intracranial tumour have recently indicated that elevation of the tentorium by growths below it is a possibility. Elsberg and Silbert[4], by the study of ventriculograms and casts made of the ventricles from post-mortem specimens, have recently demonstrated some very significant points. In subtentorial growths they found that the lateral ventricle on the side opposite to the growth was regularly more dilated than that on the same side, and that the posterior horn on the side of the tumour was consistently shorter and displaced forwards and outwards, when compared with the opposite side. Such displacement by growths in the posterior fossa can only be produced by elevation of the tentorium. Such a contention is supported by a further observation which they record, that in hydrocephalus associated with subtentorial tumours the cavity of the descending horns of the lateral ventricles (the part of that cavity situated immediately above the tentorium) was often relatively small compared with that of the anterior horns and bodies of the ventricles. Although not invariably found, this second observation by Elsberg and Silbert can only be regarded as further evidence of the possibility and the actual occurrence of elevation of the tentorium by some growths in the posterior fossa. These observations upon the size and form of the lateral ventricles on the two sides are confirmed by an example of cerebellar tumour which was kindly brought to my notice recently by my colleague, Professor J. Shaw Dunn. In this specimen the displacement of the posterior horn and the smaller size of the descending horn on the same side as the tumour are strikingly shown.

Tumours Above and Below Tentorium Cerebelli.

Having considered the exact position and communications of the great vein of Galen, it is now convenient to discuss more fully the evidence upon which to decide on the relative importance of the two possible causes of raised intracranial pressure, the two being:—

(1) Obstruction to the venous return from the choroid plexuses, with a consequent increased production of cerebro-spinal fluid, and

(2) Displacement and distortion of the brain-stem inducing obstruction to the flow of cerebro-spinal fluid through the aqueduct of Sylvius, which must in turn lead to dilatation of the lateral and third ventricles.

Since the tentorium almost divides the cavity of the cranium into two parts, the communication provided by the hiatus tentorii being largely occupied by the midbrain, there is considerable advantage in

studying, in the first place, the influences of supra- and infra-tentorial tumours separately. The supratentorial subdivision of the cranial cavity is partially divided into two by the falx cerebri. This partition, being sickle-shaped with its apex in front, separates completely the mesial surfaces of the two occipital lobes behind, while in front of its attachment to the tentorium a large communication between the two halves of the supratentorial part of the cranial cavity is left. This opening is more or less oval in shape, with its long axis antero-posterior and its vertical extent greatest in the frontal and parietal regions (fig. 1). Through the opening pressure can be transmitted across the

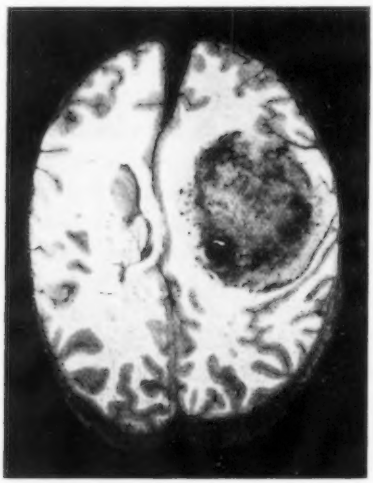

FIG. 2.—To show how a supratentorial tumour can deflect the falx.

middle line without deflection of the falx. Such pressure would be produced most likely by tumours in the lower part of the frontal and parietal lobes, and might conceivably displace the brain-stem very slightly to the opposite side and possibly downwards. It is conceivable, but not very likely, that this pressure would be sufficient to cause serious obstruction to the flow of cerebro-spinal fluid through the aqueduct. Any downward displacement would be quite as likely to cause tension upon, and so diminish the lumen of, the great vein of Galen. It is difficult, if not impossible, to believe that tumours in any other part of the supratentorial space can seriously displace the brain-stem. On anatomical grounds, such displacement seems most unlikely

to arise from growths in the occipital and hinder part of the parietal lobes, and yet it is tumours in these two situations above the tentorium which most frequently cause symptoms of raised intracranial pressure. Tumours placed in front, above, and particularly behind the opening below the falx, are liable to cause deflection of this fold to the opposite side, a condition quite commonly seen at a post-mortem examination (fig. 2). Of course it is only possible for this to occur when the tumour has grown to some size. Observing the falx from the side, it will be noticed that the risk of deflection is greater as we pass backwards from the frontal to the occipital regions, since the extent of the falx exposed to the hemisphere increases. The risk is greater in the occipital region than in any other position. With reference to this, it is interesting to recall the incidence of absence of symptoms of intracranial pressure in the fifty-nine cases spoken of in an earlier part of the paper. In tumours of the frontal and fronto-parietal regions there was no evidence of increased pressure in a third, in the parietal lobe in a fourth, in the temporo-parietal and temporo-occipital regions in a fifth; while in the nine cases of tumour of the parieto-occipital region, only one failed to exhibit signs of intracranial pressure, and the only patient without symptoms, in the series of five tumours of the occipital lobe, requires further explanation, which probably accounts for the absence of pressure symptoms. This patient died from a hæmorrhage in the opposite cerebral hemisphere, and at the time of the occurrence the occipital tumour was small; it is therefore evident that this patient died from cerebral hæmorrhage at an early stage in the development of the tumour, and before it had grown sufficiently to induce symptoms of raised intracranial pressure or to cause any deflection of the falx.

These figures certainly seem to establish a definite relationship betweeen the frequency (of the appearance) of signs of intracranial pressure and the risk of deflection of the falx. On the other hand, they do not seem to denote any relation between the occurrence of pressure symptoms and the possibility of displacement or compression of the midbrain, and such an association seems very improbable, as the frequency of symptoms is greatest in tumours of the hinder part of the parietal and occipital lobes, in which regions the midbrain is most effectually protected from pressure by the broader part of the falx.

In a series of cases published by Brain [1], in which the site of the tumour was verified at operation or post-mortem examination, similar deductions may be made, and all other reports in lists of supra-tentorial tumour which I can find manifest this association of the

frequency of symptoms of raised pressure within the cranium, and risk of deflection of the falx. The records from cases where combined ventricular and lumbar punctures have been taken also show that any obstruction of the aqueduct associated with supratentorial tumours is exceedingly rare. Recently Hodgson [6] investigated twenty-one patients suffering from tumours above the tentorium and found that there was only evidence of block in one, which was a case of pinealoma. Consequently it does not seem possible to believe that displacement or torsion of the midbrain can be an important factor in the etiology of raised intracranial pressure in supratentorial growths, whereas it does appear probable that deflection of the falx is related to the appearance of symptoms of raised pressure.

There were seventeen growths beneath the tentorium in my own series. In five of the six examples of cerebellar neoplasm, the signs of intracranial pressure appeared early and were profound. In the one patient without symptoms, who died under an anæsthetic while undergoing the operation of gastro-enterostomy, there had at no time been any suspicion of intracranial mischief. At the post-mortem examination two nodules, each about the size of a cherry, were found in the white matter of the right lobe of the cerebellum, and one about twice the size of the others projected from the under surface of the left cerebellar lobe. Histologically these tumours were all gliomata. It is difficult to understand why this patient failed to suffer from any rise of intracranial pressure—it may be that the tumours being symmetrically situated failed to displace the brain-stem, or occupying a very inferior position in the posterior fossa a certain amount of compensation could occur and the tentorium not be elevated. The condition of the ventricles in the other five cases is of considerable interest. In two of them considerable dilatation of the ventricles is reported, associated with excess of fluid in the sub-arachnoid space; in fact, at the decompression operation on one of these patients, the surgeon stated that about 5 oz. of fluid escaped on incising the dura. In a third case there was moderate distension of the ventricles without any excess of external fluid. In the other two, no obvious dilatation of the ventricles was noted post mortem: the condition of the ventricles seems to suggest that it is very unlikely there was any obstruction to the normal circulation of cerebro-spinal fluid in at least four of the five cases. In the post-mortem records of the two patients with tumours in the cerebello-pontine angle, both of whom suffered from manifestations of raised pressure for a considerable period before death, no mention is made of any displacement of the pons.

although this seems to be the situation where such a condition is most likely to arise. In one where the symptoms had been present for years and secondary optic atrophy had supervened, the lateral and third ventricles are described as being dilated to a fairly great degree, while in the other patient who had suffered from headache, vomiting and double papillœdema for at least five months, there was only moderate distension of the lateral ventricles. It would appear reasonable to anticipate more distension in this time, if any serious obstruction in the region of the aqueduct were present. Experimentally, very pronounced dilatation is known to occur in two to three weeks, but in such cases of course the obstruction is complete. The post-mortem records in neither case of angle tumour refer to any sign of obstruction, but this does not exclude its presence during life.

Of the four patients suffering from tumour of the medulla, two exhibited symptoms of raised intracranial pressure and two did not. In both the former there was obvious obstruction by the growth itself in the region of the fourth ventricle, and a consequent internal hydrocephalus was present. In the two patients without symptoms of increased pressure, one had a small "button-shaped" tumour growing from the posterior aspect of the lower end of the medulla, and in the other the growth involved the whole medulla and caused a general enlargement. From the post-mortem reports it seems possible that compensation for the increased amount of tissue in the posterior fossa might have been made by downward displacement, and this is supported, in the former case at least, by clinical evidence of tension upon the hypoglossal nerve. Any compensation by downward displacement would prevent elevation of the tentorium, and would also render lateral displacement of the brain-stem less likely to occur.

The five remaining subtentorial tumours were all situated in the pons, and in two there appears to have been no definite clinical evidence of increased pressure. In both of these the neoplasm was in the basal part, a situation most remote from the aqueduct, and where some considerable enlargement could occur without elevating the tentorium. In one of these cases it was observed at the post-mortem examination that there was an increase in the amount of fluid in the subarachnoid space; there is no clinical record of the symptoms and condition of the patient immediately preceding death, and this is particularly unfortunate as it seems possible that a raised intracranial pressure was the terminal condition. In all the three cases of pontine tumour in which symptoms of increased pressure were manifested, there was very marked

or extreme dilatation of the lateral ventricles, and in two there seems to be definite evidence of obstruction of the aqueduct; by occlusion from tumour growth in one case, and direct compression of the canal in the other. In the third, there is no record of any obstruction, but it is stated that the neoplasm was growing from the upper part of the pons and projected upwards into the transverse fissure. The two veins of Galen fuse in this fissure to form the great vein of Galen, and it is probable that the extension of the tumour would impede the venous drainage from the choroid plexuses by direct compression.

From an analysis of the seventeen cases of subtentorial tumour there does not appear to be any conclusive evidence of obstruction in the brain-stem except by the growth itself, as in two of the pontine tumours and the two medullary growths which filled the cavity of the fourth ventricle. There seems to be a complete absence of any evidence of obstruction of the aqueduct by displacement of the brain-stem except perhaps in one case of tumour in the cerebello-pontine angle, which is undoubtedly the site that is known to give rise to deflection or torsion of the brain-stem most frequently. Combined ventricular and lumbar punctures in the case of infratentorial tumours do very frequently demonstrate block. In a recent series of twenty-four, Hodgson [6] found it present in two-thirds of them. It is important to remember, however, that this does not necessarily prove the existence of block of the aqueduct, as it may quite probably be located in the region of the foramen magnum and produced by a pressure cone.

Discussion.

From the study of fifty-nine cases of intracranial tumour and the anatomical and physiological considerations of the cranial contents, it is now possible to make certain deductions.

With supratentorial tumours, lateral displacement or torsion of the brain-stem sufficient to produce obstruction of the aqueduct, must be a rare occurrence, and there is some difficulty in believing that it can ever be caused by growths in this part of the cranium. Downward displacement of the brain-stem seems more likely in the case of some supratentorial tumours, but such alteration in position would, on anatomical grounds, tend to diminish the calibre of the great vein of Galen rather than to reduce the diameter of the aqueduct of Sylvius. Furthermore, any displacement of the brain-stem is least possible in tumours situated in the hinder part of the parietal or in the occipital lobes, and yet all records show that symptoms of raised pressure are

much more frequent in the case of growths in these positions than in any other part of the supratentorial division of the cranial cavity. A neoplasm of fair size in the posterior part of the cerebrum is more liable to cause lateral deflection of the falx and consequent elevation of the tentorium than one in the frontal, fronto-parietal, or parietal regions. Therefore, in supratentorial tumours it seems probable that deflection of the falx is a more important factor than displacement or torsion of the midbrain in the production of raised intracranial pressure. It has been shown how elevation of the tentorium can lead to obstruction of the venous drainage from the choroid plexuses, and to excessive production of cerebro-spinal fluid. Therefore I maintain that there is distinctly more evidence in favour of compression of the great vein of Galen as being the cause of pressure symptoms in supratentorial growths rather than any displacement of the brain-stem. Supporters of the latter theory for explaining the symptoms of raised pressure have commonly experienced a difficulty in adapting it to all tumours above the tentorium.

Brain, in a paper to which I have previously referred, after stating that the papillœdema in cases of subtentorial growths and tumours of the ventricles, midbrain and occipital lobes, is due to the rise of intracranial pressure consequent upon obstructive hydrocephalus, goes on to say that "in the case of tumours of the frontal, parietal and temporal lobes it is caused by the local rise of intracranial pressure produced by the tumour itself." He thus divides the cases into two groups: the first group (tumours of the third and fourth ventricles, cerebellum and the one case of occipital tumour in his series) in which hydrocephalus is caused early by obstruction; and the second group (tumours of the frontal, parietal and temporo-sphenoidal lobes), in which hydrocephalus is absent or occurs later. He obtains this subdivision by reference to the relative time of onset of the vomiting, which does undoubtedly appear to be the earliest and most important sign of dilatation of the ventricles and of papillœdema. In the first group, he believes vomiting occurs very early, is one of the first symptoms to be complained of, and precedes the onset of papillœdema. In the second group, he maintains the papillœdema precedes vomiting, since there is usually "a rise inpressure within the optic sheaths before the occurrence of obstruction of the aqueduct of Sylvius." Brain does not submit any records in support of this subdivision, so it may be helpful to analyse the clinical histories of the 59 cases referred to in this paper, on these points.

It was disappointing to find that in only 16 cases (six in Group I

and ten in Group II) were accurate records available of the time of onset of vomiting and papillœdema, but in spite of this small number the information is of some value. In the six cases in Group I, vomiting preceded the papillœdema in five, and succeeded it in only one case: in two of the former, the fourth ventricle was obstructed by the growth. Of the ten cases in Group II, papillœdema preceded vomiting in four, and the latter was the earlier symptom in six. These cases do not lend very definite clinical support to the division suggested by Brain, but, excluding for the moment cases of obvious obstruction to the cerebro-spinal fluid path by tumour, they do seem to indicate that tumours in sites which predispose to the early occurrence of symptoms of intracranial pressure are most likely to cause early dilatation of the ventricles. Such an indication is not necessarily in favour of obstructive hydrocephalus as the cause of the increased pressure, since the early dilatation of the ventricles may be brought about by excessive production of cerebro-spinal fluid as well as by interference with its outflow from the ventricles.

As Brain has pointed out hydrocephalus may be produced in these cases in at least two ways: first, by an absolute obstruction of the aqueduct or fourth ventricle; and secondly, by excessive production of cerebro-spinal fluid, causing a relative obstruction, as the aqueduct would be too narrow to provide for the escape of the fluid at the same rate as its production. Occipital tumours and subtentorial tumours cause symptoms of raised intracranial pressure earlier and more frequently than frontal, fronto-parietal and parietal tumours, and these figures seem to indicate that when the symptoms occur hydrocephalus tends to supervene sooner in the former than in the latter. The figures only indicate a tendency and do not appear to me to justify a division into two groups, or to be sufficiently reliable to place much confidence with regard to site upon the relative time of the onset of papillœdema and vomiting. They do not support the belief that all cases of occipital and subtentorial growths give rise to an obstructive hydrocephalus. When we refer back to the post-mortem findings in the examples of cerebellar tumour, it will be remembered that it appeared very unlikely that in four out of the five cases manifesting raised intracranial pressure was there any obstruction to the normal circulation of cerebro-spinal fluid. This must cause us to hesitate to believe that the tendency to early dilatation of the ventricles in many subtentorial growths is an indication of obstruction by displacement of the brain-sten or similar means. My records show that hydrocephalus does occur quite frequently

in these cases without any obstruction being present. Consequently it seems safe to presume that in a large proportion the ventricular dilatation must be due to such an increased production of fluid and that it cannot escape sufficiently quickly through the narrow aqueduct. As far as I can determine, such excessive production can only be induced by impaired venous drainage from the choroid plexuses by the great vein of Galen, which vessel could be compressed by elevation of the tentorium. Neurological literature contains numerous records of cases of subtentorial growths which exhibit no narrowing of the aqueduct, even at the time of the post-mortem. As an example, the report of a case of cerebellar tumour by Rhein [10] may be quoted. It was recorded in order to illustrate the supervention of hypophysial symptoms from great distension of the third ventricle; both lateral ventricles were "enormously" distended, the third being 2 cm. in diameter and 2·5 cm. in depth, whilst the fourth was also "much distended," which must exclude any obstruction in the aqueduct by displacement or other cause. The tumour was situated in the right cerebellar hemisphere, which was about one-fourth larger than the left, and it is of interest to notice that the photographs of the brain on section show that the right lateral ventricle is less dilated than the left, which is quite possibly due to greater elevation of the tentorium on the affected side.

From this consideration of tumours below the tentorium, it seems probable that excessive production of cerebro-spinal fluid, rather than displacement and torsion of the brain-stem with consequent obstruction, is the more important factor in the production of increased intracranial pressure in subtentorial as well as supratentorial tumours. Some subtentorial tumours block the fourth ventricle, as two of the medullary growths previously referred to, and some in the cerebello-pontine angle cause such displacement of the brain-stem that obstruction to the aqueduct is possible, but excluding these it is clear that evidence of excessive production of fluid is a much commoner post-mortem finding than an obstructive hydrocephalus.

Further reference to pontine tumours is necessary. The pons lies below the hiatus tentorii rather than below the tentorium, and consequently considerable enlargement of this part of the brain-stem is possible without elevation of the tentorium. It is of interest to notice that tumours in this situation, provided they do not extend under the tentorium, may exist for long periods without giving rise to symptoms of raised intracranial pressure. My records suggest that in those cases where an increased pressure existed without extension under the

tentorium, there is evidence of obstruction of the aqueduct by direct pressure of the tumour upon or into the aqueduct, leading to marked dilatation of the ventricles. It seems likely that pontine tumours may thus cause pressure symptoms either by compressing the aqueduct and causing an internal hydrocephalus, or by extension under the tentorium, leading to elevation of this structure and consequent excessive production of fluid by interfering with the venous drainage from the choroid plexuses.

There were no examples of pineal tumour in my series, but it is highly important to consider them, as from their situation it is conceivable that they might obstruct the aqueduct by pressure downwards, or compress the great vein of Galen by extension in an upward direction. For the further discussion of these two possibilities I shall refer to the recent valuable contributions to our knowledge of pineal tumours by Horrax and Bailey. In the paper by Horrax [7] on the differential diagnosis between pineal and pontine tumours, the following important point is stressed—"the initial symptoms in all the pineal group were due to increased intracranial tension." He found that all the fifteen patients with primary pineal growths first complained of pressure symptoms, whereas only six patients out of fifteen with primary pontine tumours suffered initially from the manifestations of increased intracranial tension.

It is quite evident from the clinical records that in pineal cases the raised pressure occurs at a very early date, whatever the cause may be. The difference in time of onset of the pressure symptoms in the two groups is alleged to be due to the fact that even small pineal growths tend to block the aqueduct. It can be understood anatomically how a mass in the region of the pineal gland can press down upon the dorsal surface of the midbrain, and lead subsequently to partial or complete obliteration of the aqueduct, but it seems reasonable to suppose that pressure sufficient to induce this would be most likely to cause clinical symptoms from compression of the quadrigeminal bodies at least simultaneously with, if not before, those due to the blocking of the aqueduct. Furthermore, it must be remembered that any slight enlargement of the pineal in an upward direction must inevitably compress the great vein of Galen against the splenium. Anatomically, compression of the vein seems more likely at an early date than obstruction of the aqueduct, and without at least the simultaneous occurrence of signs of involvement of the quadrigeminal bodies with pressure symptoms, it would be rather unwise to suggest that the latter are caused by reduction in size

of the lumen of the aqueduct. When we turn to the details of the extent of twelve of the pineal tumours presented in the paper by Horrax and Bailey [8], considerable light is shed on the problem. Although the condition of the ventricular system is not recorded in every case, it is possible to conclude from the information given and the illustrations presented that in some cases there was no obstruction of the aqueduct even at the time of death. In Case 4 it is recorded that *all* the ventricles were greatly distended; in Case 11 the aqueduct is described as patent, and the fourth ventricle can be seen to be distended in the photograph. In Case 6 it is stated that there was marked dilatation of *the* ventricles, which presumably refers to all. The illustration of the brain in Case 2 seems to show some distension of the fourth ventricle, and also in Case 8, although in the latter some compression of the aqueduct is also evident. The photographs of the brain in Cases 8 and 12 suggest definitely that the aqueduct was patent, although small in Case 12. In Case 7 the aqueduct was obliterated, and could not be identified at the post-mortem examination. Although there is no evidence one way or the other in several instances, it seems probable that there was no very serious obstruction of the aqueduct in seven, and in three—possibly four—it is clear that there was no obstruction even at the time of death. In some of the reports it is noted, and perfectly demonstrated by the illustrations, that the splenium of the corpus callosum was pushed upwards and flattened, and the normal distance between the splenium and the brain-stem appreciably increased in consequence. Such upward pressure and displacement by a pineal growth must necessarily compress the great vein of Galen against the splenium. The absence of any evidence of compression of the aqueduct, even as a terminal condition, in some of these cases makes it certain that obstruction at this point cannot invariably be the cause of the symptoms of raised pressure in all instances of growth of the pineal gland. One is led to wonder whether it is ever the initial cause when noting that in Case 11 the aqueduct was found to be patent at post-mortem examination, although pressure symptoms had been present for seven months. In the face of this, of our knowledge of the position of the great vein of Galen, and of the fact that the splenium is often displaced upwards and flattened by pineal growths, it seems reasonable to conclude that in at least a proportion of these cases interference with the venous drainage was the primary cause of the raised intracranial pressure.

At post-mortem examinations marked dilatation of the lateral and third ventricles is often accompanied by such relatively slight distension

of the fourth ventricle that it may pass unnoticed, or no attention is paid to it. Such a condition is liable to be interpreted as demonstrating obstruction in the region of the midbrain. Without there being any obstruction, it is common to find the fourth ventricle relatively less dilated than the lateral. In a specimen of tumour in the parietal region recently examined I found the lateral and third ventricles enormously distended and out of proportion to the distension of the fourth ventricle, although the aqueduct was not only patent but showed some dilatation. There appear to be obvious reasons for this; in the lateral and third ventricles the production of fluid by the choroid plexuses is so great that only a proportion of it can be drained off along the aqueduct, consequently the pressure in these cavities rapidly rises and dilatation results.

It has been already noted—and it is necessary to repeat—that proof has been advanced of cerebro-spinal fluid being still produced when the ventricular pressure is considerably raised above the normal. In the case of the fourth ventricle, the production of fluid in the chamber by the small choroid plexuses in this region cannot be very great, and the pressure will depend largely upon inflow by the aqueduct, and outflow into the subarachnoid space by the foramina of Majendie and Luschka. Until the aqueduct is dilated very considerably, it seems unlikely that the inflow will greatly exceed the outflow, and consequently it is reasonable to suppose that the fourth ventricle will usually not dilate so rapidly or to the same degree as the lateral and third ventricles. It is possible that some large tumours in the posterior fossa may impede the drainage of the fluid through the foramina in the roof of the fourth ventricle. Such a condition, when it arises, would clearly cause a greater rise of pressure in the fourth ventricle and greater dilatation of its cavity. The condition of the fourth ventricle has been alluded to in some detail, as the absence of any obvious distension of this chamber, in cases where the lateral and third ventricles have exhibited definite dilatation, has been used as evidence of primary obstruction in the region of the aqueduct. I suggest that marked differences in the extent of the distension of these cavities can occur without any obstruction.

It seems possible that in the late stages an internal hydrocephalus, whether produced by an excessive amount of cerebro-spinal fluid or by an obstruction, can interfere with the absorption of the fluid and so increase the already raised intracranial pressure. Great dilatation of the ventricles compresses the cerebral tissue against the membranes and the bones of the skull, as is manifested by the flattening of the con-

volutions usually observed with a high degree of internal hydrocephalus. Such compression against the rigid walls must obstruct the normal ascent of the fluid over the hemispheres towards the superior longitudinal sinus, and so diminish absorption of the fluid which is already present in an excessive amount. This interference with absorption is clearly secondary to the hydrocephalus, and will only increase further the already raised intracranial pressure and not be the original cause of it. The accumulations of fluid at the base, particularly in the posterior fossa, which are reported in some operation and post-mortem records, may be due to this cause.

Conclusions.

(1) Evidence is submitted to show that there is very rarely any primary obstruction of the aqueduct in cases of supratentorial tumour. When it does occur, it is probably always due to direct pressure upon the aqueduct by the growth, as in some examples of pinealoma, or occlusion by the neoplasm itself. There seems to be good reason for believing that the raised intracranial pressure associated with tumours above the tentorium is originally caused by deflection of the falx, and consequent compression of the great vein of Galen, which induces an excessive production of cerebro-spinal fluid.

(2) Tumours below the tentorium may more readily obstruct the outflow of cerebro-spinal fluid from the ventricular system, but in a proportion no block is present. In the latter, at least, it seems likely that the cause of the raised intracranial pressure is due to elevation of the tentorium with consequent compression of the great vein of Galen.

(3) It seems likely that raised intracranial pressure associated with tumours within the cranium is more commonly due to compression of the great vein of Galen than to any other cause.

(4) Whilst obstruction to the venous drainage from the choroid plexuses or block in the region of the aqueduct or fourth ventricle, separately or in association, probably explain the *origin* of the raised intracranial tension, it must be mentioned that there are a number of other factors to be considered. It would appear, however, that these factors are of secondary importance and lead merely to an increase of the already raised pressure.

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THE ELECTROMYOGRAM IN MYASTHENIA GRAVIS.

BY HAROLD G. WOLFF,
HENRY KEUTMANN
AND
STANLEY COBB.

(From the Department of Neuropathology, Harvard Medical School, and the Neurological Service of the Boston City Hospital, of Boston, Massachusetts.)

THE electromyogram, by quantitatively recording the electrical currents associated with muscle contraction, is often an aid in understanding the nature of unusual or abnormal contractions. From the rhythm, frequency and height of these action currents taken when the muscle is fresh and when exhausted, the site of disease causing impaired muscle function can sometimes be defined.

Since myasthenia gravis was first described by Wilkes, in 1877, and more fully by Erb, in 1878, many theories as to its causation have been advanced [1], [2], [3], [9]. As yet none can be accepted.

It may be inferred from histopathological observations [2], [3], [4], [5] that, in addition to any possible disturbance in innervation, the muscle structure itself is altered so that normal or complete contractions would be extremely improbable. The studies of the muscle physiology [4], [6], [7], [8], [9] in myasthenia gravis further indicate that the main defect in function lies peripheral to the anterior horn cell. Furthermore, because of the characteristic appearance of the action currents during normal fatigue, it should be possible to discover whether the exhaustion of myasthenia is brought about by "excessive fatigability," as is often inferred, or by failure of contraction for other reasons.

The first attempt to study the action currents of muscle in myasthenia gravis was made by Marinesco and Athanasiu [10]. A Brocas' galvanometer was used and action currents qualitatively similar to the normal were obtained. The intensity of these currents was, however, five to six times more feeble.

The electromyographic record of the intact human muscles during exercise presents two types of waves [11]: (1) Large primary waves (Hauptwellen), to which most of the studies have been confined; and (2)

numerous smaller waves (Nebenzacken) superimposed on the larger waves. Richter [12] recognizes still a third type of wave of very small amplitude which he calls secondary waves, and which he concludes are due to impluses from higher centres.

The frequency of the primary waves during the contraction of the normal unfatigued muscle ranges from 40 to 60 per second (see Tables III to IV). As exercise is continued to the point of fatigue, the frequency of the waves decreases to as low as 25 to 30 per second, and the amplitude of the primary waves increases [13].

Herzog [14] recorded the action currents set up in the flexors of the fore-arm of a myasthenic patient when a dynamometer was pressed. He found that although exhaustion set in rapidly, the frequency of the action currents did not decrease but remained constant. The amplitude of the waves at the beginning of the work was much smaller than in the normal person and, as fatigue set in, the amplitude diminished.

Schäffer and Brieger [15] recorded the action currents of the left trapezius in a case of myasthenia gravis while the patient supported a weight of 0·5 kg. Their results were the same as those of Herzog. The frequency of the waves did not change but their amplitude became smaller. They also repeated and confirmed the other experiments of Herzog.

Our patient had the following history and physical abnormalities :—

Case.—A. G., a 30-year-old white man, was admitted to the Boston City Hospital in July, 1927.

Previous to the age of 27 he considered himself perfectly well. Two years before admission (1925) he noticed that he fatigued easily, and "was very nervous," perspired freely, had diplopia, and weakness of the wrist muscles. Nervousness, fatigability, sweating, palpitation, dyspnœa, irritability and insomnia increased steadily until the patient came to the Lahey Clinic (Boston) on April 27, 1926.

Physical examination there revealed an enlarged thyroid, exophthalmus, widened palpebral angles, swollen lids, tremor of hands and feet, a heart-rate of 120, and a blood-pressure of 145/50. He had lost almost 50 lbs.

A diagnosis of primary hyperthyroidism was made, and he was admitted to the Deaconess Hospital on May 4, 1926. The basal metabolic rate on entrance was plus 55 per cent. and his weight 116 lb. A sub-total thyroidectomy was done by Dr. Lahey.

The patient made an uneventful recovery and was discharged within three weeks. He seemed improved until, two months later, he noticed rapidly progressing weakness. On two occasions, about ten days apart, he collapsed while walking upstairs. He had difficulty in swallowing, choking spells, and

was unable to phonate clearly. When reaching for an object he seemed unable to extend his arm completely.

On re-examination at this time his skin was pale and pasty, loss of hair and the exophthalmus persisted. The pulse-rate was 70. He had very little strength and was exhausted readily.

His basal metabolic rate was found to be minus 18 per cent. Thyroxin was administered and the metabolism approached normal. X-ray plates showed no enlargement of the thymus gland.

In May, 1927 (about nine months later), he had paralysis of the superior recti muscles of the eyes, and marked exophthalmus. His basal metabolic rate was plus 27 per cent. In June he was discharged somewhat improved. He entered the Boston City Hospital for study a month later. At the time of entrance he was extremely weak and exhaustion was caused by merely sitting up for a few minutes.

In our experiments the action currents of the myasthenic muscle during voluntary contraction to exhaustion were compared with those of normal muscle under the same conditions.

Because of Marinesco's [2] interesting observation that the myasthenic reaction could be produced in the normal by hyperæmia or ischæmia, these conditions were experimentally reproduced on a normal person and the result compared with the myasthenic.

A patient with progressive muscular atrophy [1] was studied with the myasthenic. It was thought that comparison with a syndrome known to be caused by degeneration of the ventral horn cells might be of interest.

Method.

The method used was a slight modification of that described by Cobb and Forbes [13]. The right arm was fixed in an apparatus which held the fore-arm horizontally by means of a series of leather straps. The upper arm was also fixed by means of straps to a board flexed at an angle of 120°. No motion of the elbow was possible. The hand was inserted into a plaster of Paris glove, so that motion of the wrist-joint only was possible. A wire was attached to the plaster glove and connected with a pair of springs attached to an upright board. Between these springs a fine wire was stretched. The shadow of the wire fell on the aperture of the camera next to the shadow of the galvanometer string. Flexion of the wrist thus caused a pull on the

[1] A 44-year-old man complained of weakness and atrophy of the right hand and arm. There were fibrillary twitchings of small muscle groups over the entire body. The right biceps, triceps and wrist flexors were atrophied, and their deep reflexes as well as the ankle- and knee-jerks were less active on the right than on the left. There were no signs of cortico-spinal tract degeneration and no sensory disorders.

dynamometer springs, and the wire which was stretched between them cast a shadow that fell on the film and made a tracing along with the electromyographic record. The pull on the springs was calibrated, so that the work done could be approximately gauged.

The Hindle galvanometer in the regular electrocardiograph station

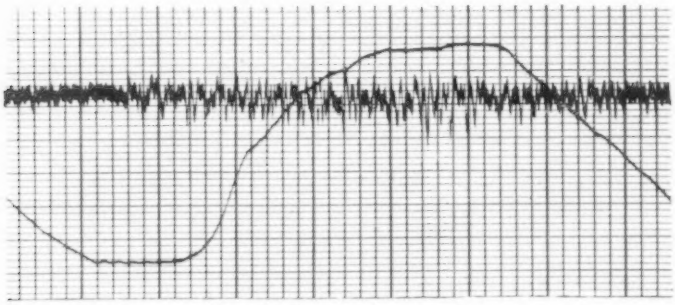

FIG. 1.—Electromyogram of normal subject (H. G. W.) (sixth contraction). The muscle contraction against the pull of the spring is recorded by the upstroke of the mechanogram.[1] The larger action currents begin before the onset of the pull, are obvious at the height and disappear with relaxation. The pull at the height of contraction is 5 kg.

[1] In all records the ventrical lines mark periods of $\frac{1}{25}$ second.

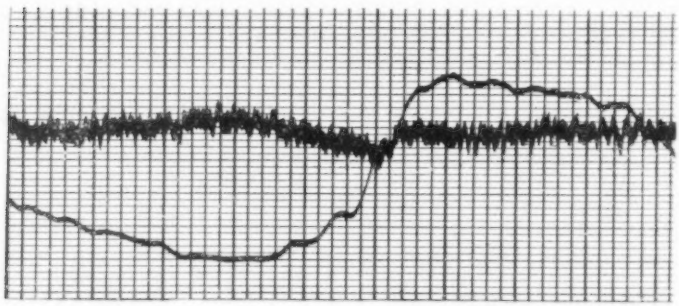

FIG. 2.—Electromyogram of patient with myasthenia gravis (sixth contraction). The record of the action currents shows less obvious difference between contraction and relaxation. The pull at the height of contraction is 266 grm.

was used. The string was adjusted to such a tension that a difference of potential of 1 millivolt would cause a deflection of 1 cm. The electrodes consisted of small zinc plates about 2 cm. in diameter, soldered to binding posts which received the wires connecting with the

instrument. The skin was thoroughly cleansed and the electrodes applied, with thick pads of cotton-wool soaked in salt solution between them and the skin. They were firmly held in place by means of wide strips of adhesive plaster. One electrode was placed over the flexors of of the fore-arm and the other, the "indifferent electrode," over the skin of the lateral surface of the arm just below the insertion of the deltoid muscle.

Electromyograms on patients and normal controls were obtained one after the other without changing the apparatus. The subject flexed the wrist against the resistance of the ergograph until extreme fatigue occurred, and during this time the electrical responses were recorded beside the curves representing the mechanical work. In the case of the patients it was practical to photograph the entire course of the exercise, because of its comparatively short duration. With the normal controls this was impracticable, but periodic exposures of several minutes' duration were made.

TABLE I.

Subject—A. G., myasthenia gravis.

Number of contractions	Frequency of primary waves	Amplitude in mm.
1	40	3-4
2	45	3-5
3	35-45	3-5
4	35-40	3-5
8	35-40	3-5
9	35-40	2-5
11	35-40	3-6
Sustained contractions of 10 seconds:		
Beginning	40-45	4-5
End	40	3-4
13	40	5-4

TABLE II.

Subject—A. G., myasthenia gravis.

Number of contractions	Frequency of primary waves	Amplitude in mm.
1	35-40	4-6
2	35-40	3-6
3	35-40	3-6
5	35-40	3-6
6	40	3-4
9	35-40	3-6
Sustained contractions of 8 seconds:		
Beginning	40	3-6
End	40-45	3-5

The frequency and amplitude of the primary waves was measured from the prints of the films. The personal equation is here significant, for the "Nebenzacken" are very confusing. Furthermore, the rhythm of action currents during contraction is subject to variation, the more powerful contractions showing more regular rhythm than

weaker ones. Therefore, minor differences were waived and attention directed to the more significant alterations. Because of these possible sources of error, the frequencies given in the tables represent the possible maxima and minima which could be derived from the same films by different observers.

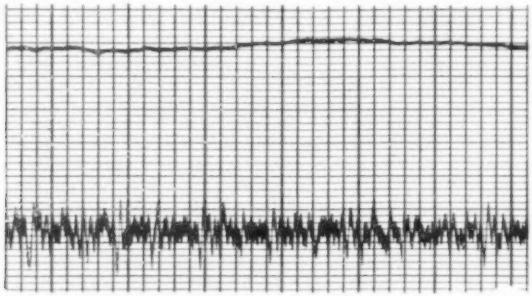

FIG. 3.—Electromyogram of normal subject. Beginning of sustained contraction. Note reduction in frequency and definite increase in amplitude.

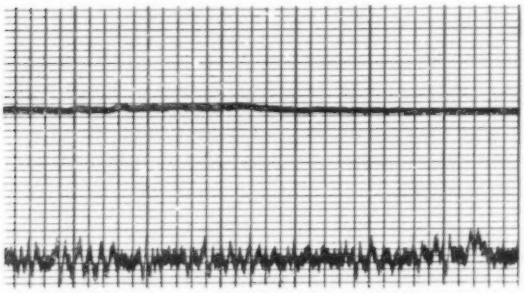

FIG. 4.—Electromyogram of patient with myasthenia gravis. Beginning of sustained contraction. Note slight reduction in frequency and slight increase in amplitude.

OBSERVATIONS.

The myasthenia patient was rapidly exhausted by the pull against the ergograph. At the height of contraction the pull was 266 grm. In Experiment 1 eleven short contractions were made, then a sustained contraction of ten seconds, after which only one more very feeble contraction, barely perceptible on the mechanogram, was possible. After recovery the experiment was repeated. This time only nine short contractions, lasting one to two seconds each, and one prolonged contraction of ten seconds, were possible.

The results of these experiments are recorded in Tables I and II, and portions of the records are represented in figures 2, 4 and 6.

At the beginning of the first experiment the frequency of the primary waves was 40 to 45 per second, and at the end it was practically the same. The amplitude at the beginning was 3 to 4 mm., and without appreciable change at end. In the second experiment the results were practically the same (see Table II).

The normal control done immediately afterwards is recorded in Table III.

TABLE III.

Subject—H. G. W, normal male.

Number of contractions	Frequency of primary waves	Amplitude in mm.
1	45-50	4-9
2	50	6-10
3	50	6-10
4	45-50	6-12
10	35-40	—
15	50	—
21	30-40	8-14
22	30-40	8-14
23	30-35	10-17

At the height of contraction the pull was 5 kg. Here there was a frequency of 45 to 50 per second at the beginning in each case, with a decrease to 30 or 35 at the end. The amplitude increased considerably as fatigue set in.

In Table IV are the results of one experiment on a normal subject, H. G. W., during a period of local hyperæmia. A blood-pressure cuff was

TABLE IV.

Subject—H. G. W., normal.

Condition—Blood-pressure cuff around upper arm and inflated so as to stop venous blood-flow.

Number of contraction	Frequency of primary waves	Amplitude in mm
1	50-55	4-7
2	50-60	4-7
3	50-60	4-7
5	55-60	5-9
7	45-50	4-9
(Work continued without recording.)		
1	50-60	4-10
2	50	4-9
3	45-50	5-11
4	45-50	5-11
5	40-45	5-12
6	40-45	4-11
7	40-50	5-10
(Work continued without recording.)		
1	45	5-7
2	40-50	5-10
3	40-50	5-10
5	40-45	5-9

placed about the upper arm of the subject just below the axilla. To produce the desired stasis the cuff was pumped to just below the arterial pressure. Electromyograms were then taken during exercise to fatigue. It was found that at the beginning of work the frequency of the primary waves ranged from 45 to 50 per second, and the amplitude was

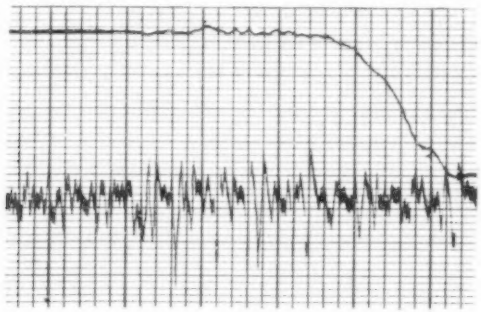

FIG. 5.—Electromyogram of normal subject. End of sustained contraction. Note reduced frequency and great amplitude.

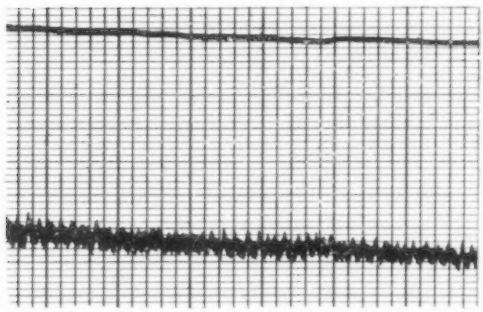

FIG. 6.—Electromyogram of subject with myasthenia gravis. End of sustained contraction. Frequency and amplitude practically constant and unchanged.

4 to 8 mm. At the end of the experiment, after extreme fatigue had set in, the frequency of the primary waves was 25 to 30 and the amplitude 6 to 12 mm.

After sufficient rest the experiment was repeated. Contractions were now begun again, and continued to fatigue and practically to

exhaustion (Table IV). This time the frequency of primary waves at the beginning of the experiment was 50 to 60 per second, with an amplitude ranging from 4 to 7 mm., while toward the end, when extreme fatigue was evident, the number of primary waves was 40 to 50 per second and the amplitude 5 to 10 mm.

After another recovery period the experiment was repeated without inflation of the blood-pressure cuff. The frequency of the waves was 50 to 60 per second at the beginning of the contractions and 30 to 40 per second at the end. The amplitude was 5 to 8 mm. in the beginning and 5 to 11 mm. at the end.

The patient with progressive muscular atrophy was examined in the same way as the myasthenic patient. One electrode was placed over one of the atrophied muscles, the flexor carpi radialis, and the other over the outer aspect of the upper arm. The results are recorded in Table V. The frequency at the beginning is from 45 to 60 per second, while at the end it is as low as 25. The amplitude at the beginning of the first experiment is 3 to 10 mm., it then goes up to 5 to 11 mm., and in the final contraction again drops. In the second experiment (Table V) the amplitude is 4 to 8 mm. at the beginning, going up to 4 to 12 mm. towards the end, but again dropping in the last contraction.

TABLE V.

Subject—T. M., progressive muscular atrophy.

Number of contraction	Frequency of primary waves	Amplitude in mm.
1	45-60	4-8
2	45-55	4-9
4	50-60	3-7
6	50-55	4-9
10	45-55	5-12
13	45	4-11
16	35-45	4-12
17	35-45	4-12
18	—	—
Lasting 15 seconds:		
Beginning	40	5-9
End	25-40	4-8

COMMENT.

The exact mechanism of the action current in intact muscle during voluntary contraction is not known. There are two reasonable conceptions. One is that each muscle action current is the electrical response on the part of the muscle to a single impulse coming to it from the motor nerve. This implies that the action currents of the nerve

and muscle have the same frequency. Dittler and Garten [16] and Gasser and Newcomer [17] have proven this for the phrenic nerve and diaphragm of animals by taking action currents off both, simultaneously. Since in fatigue the muscle action currents decrease in number, this view would lead one to infer that fatigue sets in at synapses in the cord or higher, thus letting fewer impulses travel down the motor nerve.

The other view is that the number of impulses travelling down the nerve toward the muscle is relatively high, and that the number of the muscular action currents is determined by some factor peripheral to the nerve. Cobb and Forbes [13] put forth the view that the place of adjustment is in the myoneural junction, and that the decrease in frequency during fatigue corroborates this. Their conception of delay at the myoneural junction explains the increase in amplitude of the primary waves with fatigue. The muscle fibres in the latter state cannot contract until later in the relative refractory period, and the amplitude of the response becomes greater. As an alternative to this they consider the seat of fatigue to be in the muscle fibres.

Our results on myasthenic muscle are practically in agreement with those obtained by previous observers. The primary waves of the myasthenic muscle are very small in the beginning, and the frequency of the primary waves remains constant, while in the normal individual it decreases. The amplitude remains practically constant in the myasthenic muscle, with slight increase during the first work, and then later possibly a slight tendency to decrease. Herzog [14] and Schäffer and Brieger [15] found the amplitude to decrease with exhaustion. Certainly there is no increase in amplitude. In normal muscle the amplitude increases conspicuously with fatigue.

The interpretation of these observations is that the exhaustion of myasthenic muscle is different from that of normal muscle. It is possible that the evidence of physiological fatigue could be demonstrated electromyographically if the muscle continued to contract, but that the myasthenic muscle loses its contractibility before the onset of "fatigue."

Our electromyographic records of muscle with venous stasis do not vary enough from the normal to permit us to accept the theory that excessive accumulation of acid metabolites is responsible for the myasthenic syndrome.

The electromyogram of the patient with progressive muscular atrophy differs little from the normal, with the exception of the decrease in amplitude in the final sustained contraction. Since the amplitude of the electromyogram depends, among other things, on the tension [18]

the final decrease in amplitude observed in the records may be the result of a gradual relaxation during the last fifteen to sixteen seconds. That there was relaxation is shown in the mechanical record on the film. Before the final contraction, the increase in amplitude and the decrease in frequency, as in the normal, is definite.

The essentially normal electromyogram of progressive muscular atrophy is in keeping with our conception of its essential difference from myasthenia gravis. In progressive muscular atrophy the primary degeneration is in the ventral horn cells, leading to a reduction in the number of nerve, and secondarily, of muscle units. The electrical responses of the remaining muscle units are those of normal muscle. On the other hand, in myasthenia gravis there may be a change in muscle cells, causing a generally reduced electrical response. If the muscle action be feeble only feeble action currents can result.

Conclusions.

(1) Electromyographic studies of the action currents of actively contracting muscle in a patient with myasthenia gravis reveal definite abnormalities. The frequency of the primary waves does not change with the onset of exhaustion, nor does the amplitude, which is small from the onset, increase. It usually remains small or may even decrease.

(2) Electromyographically the exhaustion of the muscle in myasthenia gravis is very different from the fatigue of normal muscle. The absence of adequate action currents indicates an absence of adequate muscle action, or contractibility, and not "excessive fatigability."

(3) Electromyographic evidence further indicates that the muscle exhaustion in myasthenia gravis is due to a fundamental defect peripheral to the ventral horn cell, and probably in the muscle cell.

We wish to express our thanks to the Director of the Thorndike Memorial Laboratory, of the Boston City Hospital, for allowing us to use the string-galvanometer, and for giving us the privilege of keeping our patient, A. G., on the Research Ward during the nine-day period of study. We also wish to thank Miss Hayes for technical assistance in the making of the records.

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Notices of Recent Publications.

Nouveau Traité de Médecine. Fascicule 18: *Pathologie du Système nerveux; Sémiologie générale.* Pp. 812. Paris: Masson et Cie. Price 85 francs. Fascicule 21: *Nerfs; Sympathique*; *Névroses.* Pp. 900. 1927. Price 85 francs.

Volume xviii of the encyclopædic "System of Medicine," which is appearing under the editorship of Professors Roger, Widal and Teissier, is the first of the four volumes to be devoted to the nervous system. It is designed on a plan favoured by the French in which disturbance of each function, as hemiplegia, ataxia, anomalies of sensation, &c., is dealt with separately, regardless of the clinical conditions with which it is associated and often with little reference to its pathology. It is obvious that this method has certain advantages in a system intended for the general practitioner, but it may also be of considerable service to the specialist who wishes to revise his knowledge.

It is impossible to refer here to all the chapters, each of which has been written by a recognized authority. Some, as those on "Coma and Apoplexy," by Janowski; "Headaches," by Lévy Valensi; and "Disturbances of Sleep," by Logre, are too short, owing probably to exigencies of space, but many chapters give detailed descriptions and satisfactory analyses of the symptoms with which they deal. Logre and Pascal, for instance, describe the commoner mental disorders from a clinical standpoint in about 100 pages, and almost as much space was allotted to the late Charles Foix for his admirable chapter on aphasia. This is modelled largely on Pierre Marie's doctrines and does not take into account much of the recent English and German work, but as a presentation of the subject to the ordinary physician it could scarcely be improved. Foix and Chavany's section on reflex disturbances is equally good. There are also chapters on paraplegia, hemiplegia, ataxia, disturbance of tone, various forms of involuntary movement and convulsions, in which the clinical features of these conditions are chiefly emphasized. Bourguignon writes on chronaxie, de Lapersonne and Velter on visual disturbances, Hautant on examination of the ears and vestibular apparatus, and Sicard on the cerebrospinal fluid.

Volume xxi deals with various nervous disorders in a more systematic manner. Nearly half its pages are occupied by a series of chapters, all written by Tinel, on traumatic and other affections of the peripheral nerves and roots, multiple neuritis and neuralgia; these all attain the high level that might be expected from the pen of this author. Short sections on vasomotor and sympathetic affections follow, and an interesting chapter by Heuyer on trophic

disturbances, in which in addition to common affections, as bedsores, perforating ulcers and von Recklinghausen's disease, rarer conditions, as angioneurotic and trophic œdema, lipodystrophia and facial hemiatrophy, are fully described. Christiansen writes well on migraine, and Klippel and Weil on epilepsy. Among other subjects dealt with are the common psychoneuroses, the choreas, tics and tetany, and the volume ends with an article by Crouzon on familial diseases of the nervous system. The authority and experience of the authors, the clear and logical manner in which they present their subjects, and the broad clinical attitude most of them adopt make the volume useful both as a textbook and a work of reference.

Die chirurgische Behandlung der Gehirntumoren. Von H. Olivecrona. S. 344. Berlin: J. Springer. 1928. Price M. 27.

This long monograph on the surgical treatment of cerebral tumours is based on the author's personal experience of only 105 cases, in 88 of which the diagnosis and localization were verified. The relatively small number of cases and the short descriptions of the clinical symptoms presented limit the value of the work, though it is instructive to study the experiences of one observer. Unfortunately the question of diagnosis by clinical methods is treated very cursorily and the principles of localization are scarcely referred to, yet the author insists that the surgeon should be his own neurologist. The large proportion of cases in which the tumour was not found is therefore not surprising, and the results are correspondingly disappointing; for instance, only five of twenty-eight patients with supratentorial gliomata survived any time.

He devotes separate chapters to the gliomata, meningiomas, acoustic tumours, &c., and gives records of all the cases of each group he observed. In conjunction with Lysholm, who has furnished some remarkably good radiograms, he discusses radiological diagnosis, ventriculography, puncture of the brain and ventricular puncture as aids in localization. The methods of surgical treatment presented offer little new, but it is of interest that he favours simple decompression in certain gliomata, and insists on the value of two or even three stages in many operations.

Die Tumoren des Gehirns, ihre Symptomatologie, Diagnostik und operative Behandlung. Von L. Puusepp. 1te und 2te Lieferung. S. 444. Tartu-Dorpat: J. G. Krüger. Price 4 dollars.

The author, who was a pupil of Bechterew and later became a "surgical neurologist," has written a very interesting contribution to the Diagnosis and Treatment of Tumours of the Brain, based on his own experience of over 500 cases. In the two parts under review he deals with supratentorial growths, and will, in the third section which has not yet been published, treat of tumours of the posterior fossa, as well as the pathology, symptomatology and principles of surgical treatment. After a short chapter on operative

technique, in which he states that he first employed general anæsthesia then local, but reverted to ether as he has found that local anæsthesia has few advantages and many disadvantages, he discusses the so-called pseudotumours and describes his own findings in the cases of this condition he has met. A short and unconvincing account of symptoms of cerebral tumour in epidemic encephalitis follows. He then passes on to deal in separate chapters with tumours of different parts of the brain, as of the frontal, central, parietal and temporal lobes, of the basal ganglia, the hypothalamic region and of the pituitary. In each section he discusses first the chief symptoms and signs on which a diagnosis can be based; then describes illustrative cases and the nature of the tumours he examined; analyses the localizing signs which his cases presented, and points out the frequency and value of each. He finally deals with the problems that confront the surgeon in the treatment and the results of his own operations. The clinical records which he publishes are adequate and make interesting reading, and his discussions on both the clinical and the surgical aspects of the subject full and instructive, but the histology of the tumours is neither up to date nor satisfactory, and many of the illustrations are poor.

Introduction biologique à l'Étude de la Neurologie et de la Psychopathologie. Par C. v. MONAKOW et R. MOURGUE. Pp. 416. Paris: Félix Alcan. 1928.

This important work presents Professor von Monakow's biological conception of the nervous system as the integrating agent for all the vital tendencies: and whether the biological principles he formulates appear entirely valid or not, they are certainly stimulating and congruent. Much of the material will be familiar to those acquainted with the writings of von Monakow and his pupils; but it has not previously been collected together as a body of doctrine, covering the disordered as well as the normal activities of the nervous system.

The more speculative portions are open to many objections, the mention of "diaschisis" and of its newly-coined counterpart "diaspasis" (denoting the mode of disintegration of function in the instinctual sphere) will sufficiently recall the criticisms that may be made of some of the notions of the Zürich school. It would be impossible to summarize, much less to examine, the original views here so lucidly presented. In many parts of the book, especially those dealing with development, the senior author speaks with magistral authority.

No countenance is given to such divisions as into mental and physical, functional and organic, physiogenic and psychogenic, nor to the sundering of embryology, anatomy, psychology, clinical investigation, pathology: the findings of these various systems are correlated with great ingenuity. The treatment is at times semi-philosophical, neologisms abound and at least one metaphysical notion, that of the Horme, the propulsive tendency of the living being towards a creative adaptation of life, is introduced; time and value are stressed as most

important factors in the integration and disintegration of function. At the same time details of development and minute structure are given their due place in the scheme and illustrated by photographs of specimens in the unrivalled collection at the Institute of Cerebral Anatomy.

The second part of the book, dealing with disintegration, will be the most interesting for medical readers; it is, however, intimately bound up with the principles enunciated in the earlier pages on integration. The disorders of the nervous system are considered first as morphological, then as secretory or humoral: under the latter heading the psychoneuroses and psychoses are discussed and their morphological basis considered to be the ecto-mesodermic barrier, i.e., essentially the choroid plexus and the ependyma. To this, put forward only as a fertile hypothesis, and to related matters such as the circulation of the cerebrospinal fluid, the last seventy pages of the book are given up. In an earlier section aphasia, apraxia and agnosia are dealt with and the views of Hughlings Jackson and Henry Head appraised.

To those who would view neurology and psychiatry widely and seek biological foundations for their studies the book will be stimulating and provocative, if not provoking.

Lewandowsky's Handbuch der Neurologie: Ergänzungsband, 2te Teil, Ite Abschnitt. *Spezielle Anatomie und Physiologie der peripheren Nerven.* Von O. Foerster. S. 190. 1928. Berlin: J. Springer. Price M. 38.

Professor Foerster furnishes us with a monograph that will be indispensable to every one who has to study and treat injuries of the peripheral nerves. The course, distribution and structure of the nerves have been hitherto described mainly by anatomists who are not familiar with the problems that face the clinician, but Foerster is a clinician who has investigated these problems with a purely practical end in view.

In the first section he deals with abnormal motor innervation of muscles and the anastomoses of motor nerves, and explains the variability of the palsies caused by nerve injuries. The distribution of the sensory nerves to the skin, bones and joints are similarily dealt with, and the author then describes the variations in the origin, anatomical course and branching of each nerve. Stoffel's theory, that every nerve consists of a series of isolated fascicles each of which carries fibres for the innervation of one muscle or the fibres of a sensory branch, has been accepted to explain many dissociated palsies, and certain surgical operations have been based on it: Foerster has re-investigated the matter and has again disproved the observations on which it is based. The last chapter is devoted to the anatomy and physiology of the brachial and lumbar plexuses and the muscular contractions obtained by electrical stimulation of the separate spinal roots. The volume is supplied with a large number of illustrations, many in colour, which are admirably reproduced.

Encéphalite épidémique, ses origines: les 64 premières observations connues. Par R. CRUCHET. Pp. 135. Paris: Doin et Cie. 1928. Price 15 frs.

It is generally accepted that von Economo was the first, in the spring of 1917, to recognize the clinical entity of epidemic encephalitis, but on the strength of a note published by Cruchet a month or so earlier, on certain forms of encephalitis observed on the French front, Professor Achard proposes, in his introduction to this book, that the disease should be known as "la maladie de Cruchet," an eponymous title which the author accepts as no other title suggested for it seems to him free from objection. He publishes his records of these cases here, and in some instances gives the after-histories of the patients. Seven cases were observed in the end of 1915 and the beginning of 1916, at Commercy and Verdun: the majority of them had had syphilis, and few are recognizable examples of encephalitis lethargica. The remaining cases were seen at Bar-le-Duc, in 1916 and 1917: they are arranged in separate groups, as mental, convulsive, hemiplegic, spinal, and polyneurotic types. It is possible that a proportion of these belonged to epidemic encephalitis, but the evidence presented here certainly justifies no change in the name of the disease.

Die epidemische Encephalitis. Von F. Stern. 2te Aufl. S. 541. Berlin: J. Springer. 1928. Price M. 56.

The second edition of this monograph supplies one of the most comprehensive and complete summaries of our clinical experience of this disease which has ravaged the world during the past ten years. It is particularly the first half of the book, which deals with its clinical manifestations in both the acute and chronic stages, that will prove of most value; here all the symptoms that may appear are accurately described and, where necessary, carefully analysed. The section on the mental disturbances that occur during, and which follow, the acute illness, is especially worthy of notice. The pathological lesions of both recent and chronic encephalitis are also fully dealt with. The section on the epidemiology of the disease might have been extended with profit, but that on its ætiology and pathogenesis is admirably written; among interesting conclusions contained in it are that the virus of encephalitis is essentially different from that of influenza, and that there is only a very indirect relation between infection by these two conditions. He suggests that the later symptoms result from the action of a virus the virulence of which is augmented by general metabolic disturbances, especially due to affection of the liver.

In the treatment of the acute stages the author employs the intramuscular injection of the serum of convalescents, and cites remarkable figures in support of the claims he makes for this method: the initial mortality is reduced and the development of later symptoms is enormously diminished. Seventy per cent. of his patients so treated were fit for work three years after infection.

The best results are obtained when this treatment can be carried out in the acute stage, but it is often useful several months after the onset. Unfortunately, no equally promising therapy of the later stages can be offered.

Degeneration and Regeneration of the Nervous System. By S. RAMON Y CAJAL, M.D., F.R.S. Translated by Raoul M. May, Oxford University Press. 2 volumes, pp. 769, with 317 illustrations. London: Humphrey Milford. 1928. Price £2 10s.

When Ramon y Cajal was given the Nobel Prize a number of medical men in the Argentine Republic raised a fund to publish a book by him. For the subject of this book he chose his studies on degeneration and regeneration of the nervous system, and by the aid of considerable re-investigation and data culled from his students and other scientists, he wrote in 1913 "an extensive monograph, original in large part." This Spanish book has now been translated into English, after being carefully revised and supplemented by the author. Although it is therefore in some respects not quite up to date, this fact scarcely detracts from its great value. It may be said at once that it is based almost entirely on the experimental study of lesions of the nervous system by means of the silver impregnation methods which Cajal has devised. In so far it is one sided. Changes in the myelin, in the Nissl granules and in the neuroglia are scantily treated in comparison with the changes in the neurofibrils of the cell body and of its expansions, and in the sheath of Schwann. But the changes in these structures are sufficiently complex, and they are described with the painstaking particularity which is so characteristic of Cajal's work.

The first volume of 396 pages deals with the peripheral nerves: the second of 364 pages with the central nervous system, the sensory and sympathetic ganglia and the retina. It is perhaps in this second part that neurologists will be most apt to meet with unfamiliar material. Although it was completed before the war, much that the war taught us of the histological changes following lesions of the brain and spinal cord is already fully described, as well as many other facts that could only have been observed in experimental material. The whole work is, indeed, full of data of which the most expert need not be ashamed to confess his ignorance. Except for one chapter, in which the author presents his theory of neurotropism, it is singularly free from theory.

The book is beautifully illustrated by the author's drawings, which depict clearly and completely almost every structure described. The translator has succeeded fairly well in giving the English equivalents for the new terms which Cajal has invented to describe his observations, and in making the book readable in spite of its abundant references to literature and meticulous detail of description. Full indices of the subjects and of the authors referred to in the text increase the value of the book as a work of reference.

Neurobiotaxis and other Subjects. By C. U. Ariëns Kappers. Pp. 76. Copenhagen: Levin and Munksgaard. London: W. Heinemann. 1928. Price 7s. 6d.

This volume contains three lectures delivered by Kappers at the University of Copenhagen. In the first of these he recapitulates the numerous observations on which he propounded the theory of neurobiotaxis, according to which simultaneously associated impressions determine the structural connections of those parts of the nervous system that receive the impressions. He shows how this hypothesis can explain the partial decussation of the optic fibres in animals with frontally placed eyes, the arrangement of the motor and sensory representations in the cortex, and other features in the anatomy of the nervous system that have been hitherto obscure. He also brings the law of mental association into relation with neurobiotaxis.

The second lecture on the phylogenetic and ontogenetic development of the corpus striatum will be of particular interest to the physician who has not the opportunity of studying personally this important but difficult matter. He shows, for instance, that the substantia nigra develops from cells that lie in the descending strio-hypothalamic tract which springs from the palaeostriatum, and that this as well as the corpus subthalamicum consequently belongs to the striatum.

The third lecture deals with the phylogenetic development of the cortex and the functions of its different layers.

A Classification of Neurological, Psychiatric and Endocrinological Disorders. Prepared under the direction of the Committee on Classification of the American Neurological Association. New York: American Neurological Association. 1928.

No one who has devoted serious thought to the subject can deny that the present nomenclature of nervous disorders is far from perfect. This publication is a commendable attempt "to introduce some sort of order into the groupings of neurological complaints, to establish a uniform, recognized terminology and to formulate a definite scheme for classification which will not be overlapping, inclusive or antagonistic." The Committee makes a preliminary division of ætiological order into developmental defects, infection, injury, intoxication, degeneration and sclerosis, neoplasm, psycho-neurosis, psychosis, obscure, vegetative and undetermined. Within each of these foregoing categories there is an anatomical subdivision. The syndromes of cerebral arteriosclerosis are dealt with separately under the group "Vascular System." A preliminary index of common disease-terms facilitates the search for the correct grouping for each particular morbid state. By thus building up a logical classification along ætiological and structural lines, the Committee deserves praise for a laudable effort at introducing order into a state of chaos. Naturally, there are drawbacks to a scheme of this sort. In the first place a

certain amount of overlap or cross-index seems inevitable. Thus, spina bifida with meningocele will be entered into two categories; osteomyelitis of the spine might be recorded as vertebral infection, abscess of the spinal cord compression paraplegia and so on. All the varieties of tetany are relegated to the cadre of parathyroid disease, although this involves a purely speculative conception of pathogenesis which in our present knowledge seems scarcely justifiable. Again, one may question the wisdom of a deliberate exclusion of nosological terms of purely symptomatic order; in an effort to be precise there is a danger of inaccuracy. Terms such as hemiplegia, chorea, Jacksonian epilepsy—though admittedly non-committal—are for that very reason of the utmost value. A given case may be characterized by some outstanding feature the precise aetiology of which remains unrevealed: for this reason one is loath to abandon such time-honoured phraseology. Especially is this true when the exact nature is so doubtful that one is forced to record the diagnosis in the form of an alternative—for example: (?) chorea, (?) tic. Schemata of a combined aetiological and anatomical type find difficulty in accommodating disorders of obscure or unknown pathology, and special miscellaneous groupings will be required. It seems that we are not yet in a position to draw up a nosological classification which is scientifically accurate and at the same time practical. The present attempt, however, is an appreciable step in the right direction, and will assist subsequent and perhaps more adequate terminological schemata.

Modern Problems in Neurology. By S. A. Kinnier Wilson. Pp. 364. London: E. Arnold. 1928. Price 21s.

Dr. Kinnier Wilson republishes in this volume several separate articles which have appeared from his pen in different journals during the last few years. All have been revised where necessary and some have been considerably modified, so that we have here not merely a handy collection of valuable contributions to neurology, but also the author's final and considered opinions on the problems with which they deal.

The subjects included in his twelve chapters are various forms of epilepsy, the narcolepsies, the older motor system and the new, disorders of motility and muscle tone, pathological laughter and crying, the dysæsthesiæ, and the Argyll Robertson pupil. The index provided will facilitate reference to any subject that may interest the reader.

Mongolism. By Kate Brousseau; revised by H. G. Brainerd. Pp. 210. London: Baillière, Tindall and Cox. 1928. Price 20s.

The authors give a very complete account of mongolism: they discuss its ætiology at some length and there is a useful chapter on the differential diagnosis of the condition. The book contains some good illustrations and a full bibliography. While it does not advance our knowledge of mongolism, it will be of interest to all those who are occupied with the congenitally defective child.

Röntgenologie des Felsenbeines und des bitemporalen Schädelbildes. Von H. W. Stenvers. S. 278, mit 324 Abbildungen. Berlin: J. Springer. 1928.

That the service of radiology to neurology has, apart from the aids of special methods as the introduction of air or opaque substances into the cranio-vertebral cavities, been disappointing is possibly in part due, as the author of this monograph emphasizes, to the fact that neurologists have given little personal attention to the subject but have relied mainly on the reports furnished by radiologists, few of whom are accurately acquainted with the problems involved, or have had much personal experience. Stevens here furnishes an example of what may be done by intensive study, and though few clinicians will be able to acquire his technical skill it is important to learn how radiograms should be interpreted and how far they can help in the localization of cerebral lesions. He makes no extravagant claims, though his reason for not including ventriculography is that he believes that properly taken and carefully studied radiograms make it usually unnecessary.

The larger part of the book deals with the changes produced in the sella turcica by different types of tumours arising within it and in its neighbourhood, and by hydrocephalus and growths situated elsewhere in the brain. In the latter case distension of the floor of the third ventricle is the chief factor, and consequently the changes are most obvious when a tumour lies near this ventricle. In the last hundred pages the changes visible in radiograms of the petrous bone are described, chiefly those associated with tumours of the ponto-cerebellar angle, but the author insists on the great care that must be taken in exposing and interpreting the photographs owing to the variability in the structure of this bone.

This book is undoubtedly a valuable contribution to a subject that will certainly be developed further in the future, and it is to be hoped that the author will soon publish his experiences in the interpretation of other radiographic changes in the skull.

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EDITOR.